

SEALEDUNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF OKLAHOMA**FILED**

MAY 24 2017

Mark C. McCartt, Clerk
U.S. DISTRICT COURTUNITED STATES ex rel.
Daron Street, M.D. and R. Steven Paulson,
M.D.

Plaintiff

v.

GENENTECH, INC.

Defendant

Case No. 17 CV 293 CVE - **MTX****FILED UNDER SEAL****COMPLAINT**
(Jury Trial Demanded)

The United States of America, through Relators Daron Street and R. Steven Paulson ("Relators"), brings this action against Genentech, Inc. under the False Claims Act, 31 U.S.C. §§ 3729 et seq. ("FCA"), to recover damages sustained by, and penalties owed to, the United States for Genentech's false claims regarding federal purchases of Herceptin, a breast-cancer drug. As a result of those false claims, the United States has paid for more Herceptin than it actually received from Genentech and has been required to purchase more vials of Herceptin than necessary for federal purposes.

NATURE OF ACTION

1. This is an action to recover damages and civil penalties on behalf of the United States for violations of the False Claims Act arising from false statements and claims made by Genentech regarding Herceptin sold to the United States.
2. Herceptin is developed, manufactured, and marketed by Genentech.

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Q. Simon?*

3. Genentech falsely stated the mass of Herceptin sold to purchasers, including the United States. Genentech labels each Herceptin vial as containing 440 mg of its active ingredient, Trastuzumab.

4. Genentech regularly manufactures and distributes vials containing less than 440 mg of Trastuzumab.

5. Either through its distributors or directly, Genentech distributed under-filled vials to Relators and other purchasers, including the United States. Genentech charges purchasers for the labeled amount of Herceptin despite knowing it does not provide the labeled amount of Herceptin in the vast majority of the Herceptin packages.

6. Through this misconduct, Genentech knowingly (1) presented, or caused to be presented, false or fraudulent claims for payment to the United States in violation of the FCA, 31 U.S.C. § 3729(a)(1), and (2) made, used, or caused to be made or used, a false record or statement material to a false or fraudulent claim for payment to the United States in violation of the FCA, 31 U.S.C. § 3729(a)(1)(B).

7. As the result of these false claims, the United States has suffered damages, and Genentech is liable for three times the damages sustained by the federal government. Genentech is also liable for a civil penalty of not less than \$10,781 and up to \$21,563 per violation after August 1, 2016 and not less than \$5,500 and up to \$11,000 per violation before August 1, 2016. 31 U.S.C. § 3729(a), as amended by 81 Fed. Reg. 26127, 26128 (2016).

JURISDICTION AND VENUE

8. This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. § 1331 and 28 U.S.C. § 1345.

9. Relators do not believe the facts and circumstances of Genentech's violation of the FCA have been publicly disclosed in a criminal, civil, or administrative hearing, or in a congressional, administrative, General Accounting Office, or Auditor General's report, hearing, audit, or investigation, or in the news media. 31 U.S.C. § 3730(e).

10. Even if public disclosure had occurred, Relators qualify as original sources under 31 U.S.C. § 3730(e)(4)(B) because they have independent knowledge that materially adds to any public disclosure and they have provided this information to the United States before filing this action.

11. This Court has personal jurisdiction over Genentech, and the Northern District of Oklahoma is a proper venue pursuant to 31 U.S.C. § 3732(a) and 28 U.S.C. § 1391(b) because Genentech transacts business in this district.

PARTIES

12. Relator Daron Street, M.D., is a resident of Oklahoma. Relator Street holds a license to practice medicine in the State of Oklahoma, is qualified, skilled and experienced in providing medical services in his specialty fields of Obstetrics & Gynecology and Gynecologic Oncology, and is an employee and officer of Oklahoma Cancer Specialists and Research Institute, LLC.

13. Relator R. Steven Paulson M.D., is a resident of Texas. Relator Paulson holds a license to practice medicine in the State of Texas, is qualified, skilled and experienced in providing medical services in his specialty fields of Hematology and Medical Oncology, and is President and Chairman of Texas Oncology, P.A.

14. Genentech is a California corporation with corporate headquarters located at 1 DNA Way, South San Francisco, California 94080. Genentech is a biotechnology company that

develops, manufactures, and commercializes medicines, including Herceptin. Genentech has sold Herceptin to Oklahoma Cancer Specialists and Research Institute, LLC and Texas Oncology, P.A. (“Relators’ Companies”) and the United States, among others. Since 2009, Genentech has been a wholly-owned part of the Roche Group. The Roche Group is a multi-national conglomerate with its headquarters in Basel, Switzerland.

15. Genentech’s reported net sales of Herceptin in the United States have been: \$1.6 billion in 2010; \$1.4 billion in 2011; \$1.7 billion in 2012; \$1.8 billion in 2013; \$2.0 billion in 2014; \$2.4 billion in 2015; and \$2.5 billion in 2016, totaling sales of \$13.4 billion over the past seven years.

FALSE CLAIMS ACT

16. The FCA imposes liability on any person who “knowingly presents, or causes to be presented, a false or fraudulent claim for payment or approval” to the federal government. 31 U.S.C. § 3729(a)(1)(A).

17. The FCA also imposes liability on any person who “knowingly makes, uses, or causes to be made or used, a false record or statement material to a false or fraudulent claim” to the federal government. 31 U.S.C. § 3729(a)(1)(B).

18. Under the FCA, “knowingly” means that with respect to the information at issue, a person (i) has actual knowledge of the information, (ii) acts in deliberate ignorance of the truth or falsity of the information, or (iii) acts in reckless disregard of the truth or falsity of the information. 31 U.S.C. § 3729(b)(1)(A). No proof of specific intent to defraud is required to show that a person acted knowingly under the FCA. 31 U.S.C. § 3729(b)(1)(B).

19. Under the FCA, the United States may recover three times the amount of damages it sustained (treble damages), plus a civil penalty for each false claim. 31 U.S.C. § 3729(a). The

civil penalty is to be not less than \$10,781 and not more than \$21,563 per violation. 31 U.S.C. § 3729(a), as amended by 81 Fed. Reg. 26127, 26128 (2016).

FACTUAL ALLEGATIONS

Genentech manufactures and markets Herceptin, a breast-cancer drug.

20. Herceptin is a patent-protected medication used to treat patients with early stage, advanced, and metastatic breast cancer and tumors that overexpress the HER2 neu receptor. Herceptin is widely used to treat breast cancer patients whose tumors overexpress the HER2 neu receptor, roughly 15-20% of breast cancer patients. For these patients, treatment with Herceptin in combination with other drugs is the standard of care because it improves their survival or decreases the chances of breast cancer recurrence. The FDA approved Herceptin as an adjuvant therapy for early stage and advanced breast cancer patients and for metastatic breast cancer patients, as well as gastric cancer patients who overexpress the HER2 neu receptor.

21. Herceptin is the most widely used cancer medication currently on the market that effectively treats metastatic breast cancer and tumors that overexpress the HER2 neu receptor.

22. Genentech develops, manufactures, and markets Herceptin.

Genentech sells Herceptin to the United States.

23. Genentech contracts with a closed network of authorized distributors to service customers through the “buy and bill” model. Through this distribution model, customers purchase Herceptin through authorized distributors. These distribution partners agree to distribute only products purchased directly from Genentech and not distribute Herceptin through secondary channels.

24. Since 1998, Relators’ Companies have purchased Herceptin to use in the treatment of their patients.

25. Genentech maintains a list of authorized distributors for federal purchasers. *See* Genentech Herceptin Product Distribution Webpage, *available at* <https://www.genentech-access.com/hcp/brands/herceptin/learn-about-our-services/product-distribution.html> (last visited May 16, 2017), Ex. 1. These distributors include AmerisourceBergen Drug Corporation, Cardinal Health Specialty Distribution, Dakota Drug, DMS Pharmaceutical, and McKesson Plasma and Biologics. *See id.*

26. In the third quarter of 2004, 1% of Herceptin sales were to federal facilities. *See* Abt Associates Inc., Sales of Drugs and Biologicals to Large Volume Purchasers at 19 (Exhibit 4.1), 20 (Exhibit 4.2) (Dec. 15, 2005) (Ex. 2 hereto), *available at* <https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Reports/downloads/wrobel3.pdf>.

27. Since July 1, 2008, the United States has entered into over 50 contracts and grants to purchase Herceptin. USASpending.Gov Data Search for Herceptin (Ex. 3), *available at* <http://tinyurl.com/USASpendingGovHerceptin> (last visited May 16, 2017). For example:

- a. On April 11, 2012, the Department of Defense (“DOD”) entered in to a \$40,686.47 contract with Cardinal Health to purchase Herceptin 440 MG MDV. (Award No. SPM2DX10D0028). *See* USASpending.Gov Data Search for Herceptin. (Ex. 4.)
- b. On June 23, 2014, the DOD entered into a \$30,216.41 contract with Cardinal Health to purchase Herceptin 440 MG MDV 1S. (Award No. SPM2DX10D0028). *See* USASpending.Gov Data Search for Herceptin. (Ex. 5.)
- c. On August 4, 2014, the DOD entered in to a \$66,570.05 contract with Cardinal Health to purchase Herceptin 440 MG MDV 1S. (Award No. SPM2DX10D0028). *See* USASpending.Gov Data Search for Herceptin. (Ex. 6.)

28. On September 30, 2016, the United States Department of Veterans’ Affairs (the “VA”) awarded Genentech a five-year contract worth \$3,850,225,230.00 for the purchase of

Herceptin. *See* National Acquisition Center (CCST) Award Page (Ex. 7); FedBizOpps Award Notice (Ex. 8), *available at* <https://www.fbo.gov/index?s=opportunity&mode=form&tab=core&id=a7acd54cd420422dc4d372a529f1e69c> (last visited May 16, 2017).

29. At least as early as December 2014, the VA included a monograph for Herceptin in its National Formulary. *See* National Drug Monograph for Trastuzumab (Herceptin) (Ex. 9), *available at* https://www.pbm.va.gov/clinicalguidance/drugmonographs/Trastuzumab_HERCEPTIN_monograph.pdf (last visited May 23, 2017).

30. Other specific federal purchases will be identified in Genentech's records and the records of Genentech's authorized distributors.

The Herceptin Label makes inaccurate claims regarding the contents of the vial and concentration of reconstituted Herceptin.

31. Herceptin is manufactured as a lyophilized (dehydrated and "freeze-dried" powder) medicine which is delivered in vials, labeled by Genentech as containing 440 milligrams (mg) of Trastuzumab (the active ingredient in Herceptin). The Herceptin product is mixed with a liquid (diluent), also provided to end users by Genentech. The mixing process is accomplished by injecting the diluent into the vial containing the lyophilized Herceptin.

32. This mixing process reconstitutes each vial of Herceptin cake into a multi-dose liquid solution.

33. In 1998, as a part of its lengthy Biologics License Application ("BLA") for Herceptin, Genentech submitted to FDA a proposed label and Prescribing Information (the "Label") for Herceptin. The FDA approved the BLA.

34. The 1998 Label claimed that the vial contained 440 mg of Trastuzumab and provided a Preparation for Administration section that instructed: "Each vial of HERCEPTIN

should be reconstituted with 20mL of [Bacteriostatic Water for Injection] as supplied, to yield a multi-dose solution containing 21 mg/mL Trastuzumab.”

35. Genentech has modified the Herceptin Label several times since 1998.

36. Each Herceptin Label has claimed that the vial contained 440 mg of Herceptin and that reconstitution with 20 mL of Bacteriostatic Water for Injection would yield a multi-dose solution containing 21 mg/mL of Herceptin.

37. With the sale of each vial of Herceptin to the United States, Genentech claims that (1) the vial contains 440 mg of Herceptin, and (2) if a healthcare provider follows the instructions for reconstitution on the Herceptin Label, the resulting multi-dose liquid solution is concentrated at a density of 21 mg of Herceptin per milliliter (mL) of solution.

38. 440 mg reconstituted into a liquid solution with a density of 21 mg/mL would result in 20.952 mL of liquid solution: 440 mg divided by 21 mg/mL.

The vast majority of Herceptin vials sold in the United States contain less drug than the labeled 440 mg.

39. Relators have discovered that Genentech regularly fills vials sold in the United States with less than 440 mg of Herceptin.

40. Approximately 90% of the lots of Herceptin released in the United States contained less than 440 mg of Herceptin.

41. Given the systematic under-filling of vials, many Herceptin vials purchased by the United States contained less Herceptin than the amount claimed by Genentech and for which the United States paid.

The concentration of reconstituted Herceptin is 22 mg/mL, not 21 mg/mL.

42. Relators have discovered that, in 2002, Genentech’s Herceptin Production Engineer stated in an internal Genentech email that the actual concentration of reconstituted Herceptin was

21.8 mg/mL, not the 21 mg/mL claimed by Genentech's Label. *See* Email from Tom White to Olivia Ware (Sept. 25, 2002) (Ex. 10).

43. Healthcare providers are required to follow the Label instructions in calculating the proper dosage of Herceptin to give their patients. The United States thus relies on Genentech's claim regarding the concentration of the reconstituted Herceptin solution when determining the proper dosage to administer to each patient. For example, a person weighing 75 kg should receive 200 mg of Herceptin for her initial dose. To administer 200 mg of Herceptin, the United States would provide 9.52 mL of liquid solution (*i.e.*, 200 mg divided by 21 mg/mL). If the Label stated a concentration of 21.8 mg/mL, then the United States would provide the patient 9.17 mL of the liquid solution (*i.e.*, 200 mg divided by 21.8 mg/mL).

44. By misstating the concentration, Genentech causes Relators and other purchasers—including the United States—to administer more Herceptin than necessary to patients and to purchase more Herceptin than they would otherwise purchase.

45. If Genentech stated the accurate concentration of the reconstituted Herceptin solution on the Herceptin Label, Relators and the United States would purchase fewer Herceptin vials.

Herceptin vials do not yield 20.952 mL of liquid solution.

46. Relators have discovered that when healthcare providers follow the Preparation of Administration instructions provided by Genentech, a vial of Herceptin does not yield 20.952 mL of liquid solution.

47. When they follow Genentech's instructions, Relators' Companies cannot obtain more than 20.2 mL of liquid solution from a vial of Herceptin.

48. Relators and the United States receive less drug product than the claims on Genentech's label promise they should receive.

Genentech knew the claims on the Herceptin Label were false.

49. Genentech knew that most Herceptin vials sold in the United States did not contain 440 mg of Herceptin.

50. At a hearing in related litigation, Genentech's lead counsel stated that Genentech had produced to the plaintiffs certificates of analysis showing that "in every lot [of Herceptin] released in the United States, we were below 440. Almost every. Ninety percent, I think they said. *So we knew.*" (emphasis added). Nov. 17, 2016 Discovery Hr'g Tr. at 43:9-12, in *In re Genentech MDL*, Case No. 16-md-2700 (N.D. Okla. Nov. 17, 2016) (Ex. 11).

51. Genentech's lead counsel further stated that Genentech had produced its "own manufacturing documents that show we're below 440, in [plaintiffs'] words, 90 percent of the time." *Id.* at 43:16-18.

52. Genentech also knew that it misstated the concentration of Herceptin. In 2002, Genentech's Herceptin Production Engineer stated the actual concentration of reconstituted Herceptin was 21.8 mg/mL, not the labeled 21 mg/mL. (*See* Ex. 10.)

53. Because Genentech knew that the vast majority of Herceptin vials sold in the United States do not contain 440 mg of Herceptin, it also knew that the vials would not yield 20.952 mL of liquid Herceptin solution. Similarly, because Genentech also knew that its Label did not accurately state the concentration of reconstituted Herceptin, it knew that the vials would not yield 20.952 mL of liquid Herceptin medicine.

CLAIMS FOR RELIEF

Count 1:

Violations of the False Claims Act, 31 U.S.C. § 3729(a)(1), by Submission of False Claims

54. Relators re-allege and incorporate herein by reference paragraphs 1 through 53.

55. By representing to the United States that each Herceptin vial contained 440 mg of Herceptin when Genentech knew the vast majority of Herceptin vials sold in the United States contain less than that amount, Genentech knowingly caused false or fraudulent claims for payment to be presented to the United States in violation of the FCA, 31 U.S.C. § 3729(a)(1). As a result, the United States paid false claims that were inflated or not entitled to be paid.

56. In addition or in the alternative, by representing to the United States that after preparation according to Genentech's instructions, reconstituted Herceptin is concentrated at 21 mg/mL when Genentech knew the concentration level of 21mg/mL was not accurate, thus requiring the United States to purchase more Herceptin than it needed, Genentech knowingly caused false or fraudulent claims for payment to be presented to the United States in violation of the FCA, 31 U.S.C. § 3729(a)(1). As a result, the United States paid false claims that were inflated or not entitled to be paid.

57. In addition or in the alternative, by representing to the United States that each Herceptin vial would yield 20.952 mL of liquid solution when Genentech knew the vials would yield less than that amount, Genentech knowingly caused false or fraudulent claims for payment to be presented to the United States in violation of the FCA, 31 U.S.C. § 3729(a)(1). As a result, the United States paid false claims that were inflated or not entitled to be paid.

58. As a result of these false claims, the United States suffered damages in an amount to be determined at trial. Pursuant to the FCA, Genentech is liable for three times the damages

sustained by the federal government, plus a civil penalty of not less than \$5,500 and up to \$11,000 for sales prior to August 1, 2016 and for higher amounts after August 1, 2016. 31 U.S.C. § 3729(a), as amended by 81 Fed. Reg. 26127, 26128 (2016).

Count 2:

False Claims Act, 31 U.S.C. § 3729(a)(1)(B), by Making or Using False Records or Statements Material to a False or Fraudulent Claim

59. Relators re-allege and incorporate herein by reference paragraphs 1 through 58.

60. By representing to the United States that each Herceptin vial contained 440 mg of Herceptin when Genentech knew the vast majority of Herceptin vials sold in the United States contain less than that amount, Genentech knowingly made, used, or caused to be made or used, a false record or statement material to a false or fraudulent claim for payment to the United States in violation of the FCA, 31 U.S.C. § 3729(a)(1)(B). As a result, the United States paid false claims that were inflated or not entitled to be paid.

61. In addition or in the alternative, by representing to the United States that after preparation according to Genentech's instructions, reconstituted Herceptin is concentrated at 21 mg/mL when Genentech knew the concentration level of 21 mg/mL was not accurate, thus requiring the United States to purchase more Herceptin than it needed, Genentech knowingly made, used, or caused to be made or used, a false record or statement material to a false or fraudulent claim for payment to the United States in violation of the FCA, 31 U.S.C. § 3729(a)(1)(B). As a result, the United States paid false claims that were inflated or not entitled to be paid.

62. In addition or in the alternative, by representing that each Herceptin vial would yield 20.952 mL of liquid solution when Genentech knew the vials would yield less than that amount, Genentech knowingly made, used, or caused to be made or used, a false record or

statement material to a false or fraudulent claim for payment to the United States in violation of the FCA, 31 U.S.C. § 3729(a)(1)(B). As a result, the United States paid false claims that were inflated or not entitled to be paid.

63. As a result of these false claims, the United States suffered damages in an amount to be determined at trial. Pursuant to the FCA, Genentech is liable for three times the damages sustained by the federal government, plus a civil penalty of not less than \$5,500 and up to \$11,000 for sales prior to August 1, 2016 and for higher amounts after August 1, 2016. 31 U.S.C. § 3729(a), as amended by 81 Fed. Reg. 26127, 26128 (2016).

Potential Damages

64. Relators cannot determine the amount of actual damages owed by Genentech to the United States until more information is obtained through discovery. However, based on publicly available information reviewed by Relators to date, those damages will be substantial.

65. For example, in September 2016, Genentech and the VA entered into Federal Supply Schedule contract number V797D-60724 for the sale of Herceptin. (*See* Exs. 7, 8.) Genentech agreed to sell Herceptin to the VA at a price of \$4,000.34 per vial. (Ex. 7.) According to the Award Notice, the VA expects to spend approximately \$3,850,225,230.00 over the next five years to purchase Herceptin. (Ex. 8.) This equates to an average expected cost of \$770 million per year.

66. Based on these estimated costs, the VA anticipates purchases of 192,483 vials of Herceptin per year (\$770 million at \$4,000.34 per vial). This estimate presumably is based on data from the VA's past purchases of Herceptin.

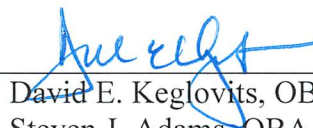
67. Assuming VA purchases at those levels, under-filling vials of Herceptin by 3% would cause damages of \$23.1 million per year, to be trebled under the FCA.

68. Again utilizing these estimates, the VA alone purchases approximately 1,154,898 Herceptin vials over a six-year period. An FCA penalty of \$11,000 per vial would support a total penalty of \$12,703,878,000.00.

REQUEST FOR RELIEF

WHEREFORE, Relators, on behalf of the United States, request judgment be entered in favor of the United States and against Genentech, awarding treble damages, all civil penalties permitted per false claim, and awarding Relators the maximum percentage of recovery as well as their costs incurred in this action, all together with pre- and post-judgment interest, and any and all other and further relief as the Court may deem just and equitable.

DATED: May 24, 2017



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ATTORNEYS FOR PLAINTIFF

EXHIBIT 1



MENU

Herceptin® (trastuzumab) ▼

Herceptin Distribution

Authorized Distributors (.tab-1)

Buy and Bill (.tab-2)

Spoilage Replacement Program (.tab-3)

Authorized Distributors

Genentech has contracted with a network of authorized distributors to service customers who choose to purchase Herceptin through the buy and bill model. Through the streamlined distribution model, customers purchase Herceptin through authorized distributors that have made a commitment to product integrity. These partners have agreed to distribute only products purchased directly from Genentech and not distribute Herceptin through secondary channels.

Distributors for Federal Accounts

Distributor

Telephone

Fax

AmerisourceBergen Drug Corporation	844-222-2273	816-464-4140
Cardinal Health Specialty Distribution	800-926-3161 270-219-6000 (KY) 501-707-2800 (AR)	N/A
Dakota Drug	866-210-5887	763-421-0661
DMS Pharmaceutical	877-788-1100	847-518-1105
McKesson Plasma and Biologics (MPB)	877-625-2566	888-752-7626

Distributors for Hospitals

+

Distributors for Physician Offices and Federally Qualified Health Centers

+

Distributors for Authorized Specialty Pharmacies

+

Distributors for Puerto Rico

Genentech does not influence or advocate the use of any one specialty distributor or specialty pharmacy. We make no representation or guarantee of service or coverage of any item.



Learn About Treatment With Herceptin >
(<http://www.herceptin.com/hcp/>)



Download the forms you need to get started
View Herceptin Forms and Documents >
(</hcp/brands/herceptin/forms-and-documents.html>)



Latest Updates

Form:

Statement of Medical Necessity (SMN)

Learn More > (</hcp/brands/herceptin/forms-and-documents.html>)

Form:

Patient Authorization and Notice of Release of Information (PAN)

Learn More > (</hcp/brands/herceptin/forms-and-documents.html>)



(<https://www.gene.com>)

Contact Us (</hcp/brands/herceptin/contact-us.html>) |

Site Map (</hcp/brands/herceptin/site-map.html>) |

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Terms & Conditions (<http://www.gene.com/terms-conditions>)

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For assistance, call
(888) 249-4918

Patient Assistance Tool >
(</hcp/brands/herceptin/find-patient-assistance.html>)

EXHIBIT 2



Abt Associates Inc.

Sales of Drugs and Biologicals to Large Volume Purchasers

Final Report

Cambridge, MA
Lexington, MA
Hadley, MA
Bethesda, MD
Chicago, IL

**Contract #500-00-0049
Task Order 1**

December 15, 2005

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Executive Summary

Background and Methods

The Medicare Prescription Drug, Improvement, and Modernization Act (MMA) of December 2003 reformed CMS' payment approach for the prescription drugs covered by Part B of Medicare. As of January 1, 2005, payment for these drugs is a function of "average sales price"(ASP), a manufacturer-reported measure that is based on actual manufacturer revenues. The specific payment amount is 106 percent of the ASP. As part of this reform, the MMA required the Secretary of Health and Human Services (HHS) to submit a report to Congress on the sales of drugs and biologicals to large volume purchasers (LVPs) to determine whether prices paid by LVPs are similar to the prices available to prudent physicians and to assess whether exclusion of LVPs would affect the computation of a manufacturer's average sales price. The current study is intended to provide background to the Secretary of HHS as a basis for preparing the report to Congress.

For this study, the project team conducted interviews with market participants, analyzed primary invoice data submitted by the purchasers, and analyzed secondary data from the IMS Health's National Sales Perspectives database (NSP). The project team also requested data on ASP by class of trade from manufacturers, but no manufacturer complied with this request. The project data came from months early in, and, in some cases, preceding the ASP period; the interview and invoice data were collected in the spring of 2005 and the IMS data draws on invoices from the third quarter of 2004.

Study Limitations

In order to undertake any study, one must have access to adequate data. While the project team made a significant effort to acquire the best available data for this report, the available data had significant limitations that prevented the study from drawing conclusions on the primary questions of interest. The data limitations included:

- Sample sizes were small in both the interviews and the primary invoice data, due to a combination of low target numbers of respondents and low response rates. Ultimately, the project relied on 36 interviews and on invoices from six physicians' offices and twelve hospitals.
- Some interviews were incomplete or difficult to interpret, due to the sensitivity and complexity of the material.
- Data on the net acquisition cost by type of purchaser or average sales price by type of purchaser were not available due to a number of factors discussed below.
- By nature, both the primary and secondary invoice data lacked information on special pricing terms and manufacturer rebates. A provider's net acquisition cost is its invoice price less any special pricing terms and rebates. A manufacturer's ASP is its average invoice price less the average of any wholesaler or distributor mark-ups less the average of all purchaser and non-purchaser rebates.
- The secondary invoice data had additional limitations. It was aggregated according to broad classes of trade, many of which contained multiple sub-categories of purchasers believed to

receive differential pricing. It also consisted of *average* prices only and did not provide measures of price dispersion within classes of trade.

- No manufacturer submitted complete data on ASP by class of trade for a focus drug.
- The study data were collected prior to or very shortly after the implementation of ASP-based payment. The market for the drugs covered by Part B of Medicare is very dynamic and is still adjusting to the new environment created by the MMA.
- Classes of trade were not well defined. The definitions of the various types of classes are not clear and consistent among market participants, and market participants' working definitions of the classes of trade are not necessarily consistent with the MMA's implied concepts of prudent physicians and large volume purchasers.

Due to these limitations, this study was not conclusive on the key questions of whether physicians' net acquisition costs were comparable to large volume purchasers' net acquisition costs and the effect on ASP of eliminating large volume purchasers from the calculation.

Research Questions and Findings

The study was organized according to seven research questions. These questions and the associated findings follow:

1. *What shares of the top drugs covered by Part B of Medicare are purchased by various types of purchasers?*

Interview and secondary data concurred that the major purchasers of the top drugs covered by Part B of Medicare were physicians and hospitals, not GPOs, HMOs, or PBMs. The secondary data analysis did offer volumes by class of trade for the categories of purchasers defined in the IMS data. For most of the 25 study HCPCs, the class of trade with the largest share of the market was clinics (including physicians' offices); hospitals were usually the class of trade with the second largest market share.

2. *Do different types of purchasers face the same net acquisition costs for Part B prescription drugs?*

The study was unable to obtain data on net acquisition costs by type of purchaser. However, the interviews suggested that different types of purchasers face different net acquisition costs and the primary and secondary invoice data suggested that different purchasers face different invoice prices for the prescription drugs offered by Part B of Medicare examined in this study. Both comments made in interviews and a review of the secondary data indicated that for the sample of drugs examined in this study the main source of variation in net acquisition costs/average invoice prices was different purchasers paying different prices for the same drug (NDC-11) within a molecule, not different purchasers choosing different drug products within that molecule. The interviews also yielded a list of purchaser-level drivers of net acquisition costs, including class of trade, ability to influence market share, volume, and purchaser expertise.

3. *Which purchasers face lower and higher net acquisition costs?*

While the study found that differences in net acquisition costs/invoice prices existed, we did not find conclusive and consistent evidence concerning whether physicians were disadvantaged relative to large volume purchasers. The primary data collection (both interviews and invoice data) offered some anecdotal information suggesting that physicians paid higher net prices than hospitals for some

drugs. In contrast, the secondary data showed that as a general rule, clinics (the class of trade that included physicians) faced the lowest average invoice prices per dose of all the major classes of trade for most of the study HCPCs.

4. *If differences in net acquisition costs exist, do they vary by drug?*

Both the interviews and the secondary data analysis clearly indicated that differences in net acquisition costs/average invoice prices varied by drug. The interviews highlighted that the presence of therapeutic or generic competition were critical factors.

5. *Would differences in net acquisition costs for different types of purchasers be reflected in ASP if it were calculated by class of trade?*

As a conceptual matter, ASP differs from net acquisition cost because it does not account for wholesaler and distributor mark-ups, which are part of net acquisition costs, and because it is reduced by non-purchaser rebates, which are not part of purchasers' net acquisition costs. Interview respondents suggested that wholesalers' and distributors' margins were small, the implication being that ASP, if calculated by class of trade, would be likely to reflect the differences in net acquisition costs by class of trade.¹

6. *Are there differences in ASP when it is calculated for different types of purchasers?*

The study was not conclusive on this point. No manufacturer submitted complete data on ASP by class of trade for a focus drug, and no other market participant was in a position to comment directly on this subject.

7. *Does excluding hospitals, HMOs, or other large volume purchasers affect ASP calculations?*

Due to the lack of information on ASP by class of trade, the study was not conclusive on this point.

Discussion

The sensitive and confidential nature of prescription drug pricing makes this an extremely challenging topic to research. This study used the best data available at this point in time but was ultimately inconclusive due to data limitations. At this point in time, market participants are not willing to provide price data at a sufficient level of detail to permit a thorough analysis of net acquisition costs and average selling prices by class of trade.

To be successful, future work on net acquisition costs and ASP for the drugs covered by Part B of Medicare must be based on adequate data that overcome some or all of the limitations described above. Any continuing work on this topic must also recognize that the market for prescription drugs, in general, is very dynamic and has just begun to adjust to the new coverage and pricing environment created by the MMA.

¹ Respondents at one manufacturer emphasized that, for their product, non-purchaser rebates were large and drove a wedge between net acquisition costs and ASP.

1.0 Introduction

1.1 Motivation for Study

Section 303(c)(2) of the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) of December 2003 reformed CMS' payment approach for the prescription drugs covered by Part B of Medicare. As of January 1, 2005, payment for these drugs is a function of "average sales price" (ASP), a manufacturer-reported measure that is based on actual manufacturer revenues. The specific payment amount is 106 percent of ASP. Prior to 2005, CMS' payment approach for these drugs was based on "average wholesale price," which is a list price as opposed to a transaction price. This change was intended both to yield a payment approach that was a more accurate reflection of providers' net acquisition costs and to lead to an appropriate reduction in Medicare expenditures.

As its name would suggest, ASP is an *average* sales price and may not represent individual purchasers' net acquisition costs to the extent that there is variation in such costs. Some have voiced concern that large volume purchasers might face lower costs than physicians for Part B covered drugs and that, if this were the case, then ASP-based payment might not provide adequate reimbursement to physicians.

To address this concern, the MMA required the Secretary of Health and Human Services (HHS) to submit a report on the sales of drugs and biologicals to large volume purchasers (LVPs).² The purpose of the required report was to determine whether prices paid by LVPs were similar to the prices available to prudent physicians and to assess the impact of excluding LVPs from the computation of a manufacturer's average sales price (ASP) for drugs and biologicals covered under Medicare Part B. The current study provides background to the Secretary of HHS as a basis for preparing the report to Congress. The remainder of this chapter presents the study questions; chapter 2 details methods; chapters 3, 4, and 5 describe findings, and chapter 6 concludes.

1.2 Study Questions

The language in the MMA required that the project's study questions address two related pricing concepts: "prices paid" or "net acquisition costs" and "average sales price" or "ASP."

For the purposes of this analysis, we considered net acquisition costs to have three components. The first is the invoice price, which is the price shown on the invoice between the purchaser and the supplier. Second are any special pricing terms between the purchaser and supplier that further reduce the purchaser's acquisition costs but are not shown on the invoice; these might be prompt pay discounts, volume discounts, or economic consideration. The final component is the purchaser rebate, which is a payment from the manufacturer to the purchaser. Typically rebates are not paid at the time of sale but are paid on a periodic basis as a reward for meeting goals related to volume or market share.

While net acquisition costs and ASP are very similar, they are not identical. Roughly speaking, ASP is equal to the manufacturer's revenue divided by units sold. Thus, ASP differs from net acquisition cost in that it excludes any mark-ups or costs added by wholesalers or other market intermediaries.

² A list of all acronyms is provided in Appendix A.

Also, ASP includes rebates to non-purchasers such as pharmacy benefits managers (PBMs) or health maintenance organizations (HMOs).³

In addition to addressing the pricing concepts of net acquisition costs and ASP, the project's study questions had to operationalize the concept of "large volume purchasers." Language in the MMA defined this concept in terms of classes of trade rather than in terms of volume *per se*; the project followed suit. The MMA specifically mentioned HMOs, and PBMs; these groups were included in our study. In addition, our study included hospitals, because they are major purchasers of Part B drugs and large relative to many physician practices; we also included wholesalers and group purchasing organizations (GPOs), because they are important participants in the markets for the drugs covered by Part B. While the emphasis in the study was on classes of trade, we also sought to explore the contribution of *volume* to net acquisition costs and average sales price.

In response to the mandate in the MMA and taking these considerations into account, the current study defined seven research questions:

1. ***What shares of the top drugs covered by Part B of Medicare are purchased by various types of purchasers?*** The impact of excluding various types of purchasers from the ASP calculation is the product of the excluded group's share of doses and the difference in ASP between the excluded groups and the remaining purchasers, thus it is important to understand different classes of trade's share of doses in addition to their ASPs.
2. ***Do different types of purchasers face the same net acquisition costs for Part B prescription drugs?*** Net acquisition cost is the first of the pricing concepts mentioned above.
3. ***Which purchasers face lower and higher net acquisition costs?*** The MMA called for a focus on the comparison between physicians and large volume purchasers.
4. ***If differences in net acquisition costs exist, do they vary by drug?*** The answer to this question has the potential to shed light on the drug-level drivers of variation in acquisition cost as well as to guide future research to account for these differences.
5. ***Would differences in net acquisition costs for different types of purchasers be reflected in ASP if it were calculated by class of trade?*** As noted above, ASP excludes mark-ups and includes non-purchaser rebates. The report seeks to understand the magnitude of these components and thus whether addressing discrepancies at the level of ASP would also serve to address discrepancies at the level of net acquisition costs.
6. ***Are there differences in ASP when it is calculated for different types of purchasers?*** ASP is the second essential pricing concept defined in the MMA.
7. ***Does excluding hospitals, HMOs, or other large volume purchasers affect ASP calculations?*** As a practical matter, including or excluding LVPs when calculating ASPs is much more important if this choice significantly affects the ASP for one or more key drugs.

³ Although there are some exceptions to this rule, PBMs and HMOs typically do not acquire prescription drugs. However, both PBMs and HMOs influence drug utilization via preferred drugs lists, formularies, and other utilization management tools. As a result, manufacturers are willing to pay rebates to PBMs and HMOs in order to create incentives for PBMs and HMOs to encourage the use of their products.

2.0 Methods

2.1 Overview of the Research Design

The project team analyzed these questions using both primary and secondary drug pricing data. The project team conducted interviews with four categories of respondents: (1) experts, (2) manufacturers of the drugs covered by Part B of Medicare, (3) market intermediaries (wholesalers and GPOs), and (4) purchasers of the drugs covered by Part B of Medicare (physicians, hospitals, HMOs and PBMs). We also requested written data on drug pricing from all groups except the experts. The primary data provided market participants' experience and perspectives on the research questions. The primary data collection effort was also designed to yield qualitative and quantitative information about special pricing terms (such as delayed payment terms and other discounts not listed on the invoice) and manufacturer rebates, neither of which were incorporated into the secondary data, and to focus specifically on Medicare Part B drugs.

The source of secondary data on the acquisition costs of prescription drugs by class of trade was the National Sales Perspectives data (NSP), available from IMS health. The project data is summarized in Exhibit 2.1 below.

Exhibit 2.1: Overview of Project Data

Primary Data: Interviews and Written Data			
Respondent Category	Interviews		Written Data Requested
	N Target	N Complete	
Experts	8	6	None
Manufacturers	9	3	Average selling prices by class of trade
Market Intermediaries	14	4	
<i>Wholesalers</i>	7	1	Discounts and rebates by class of trade
<i>Group Purchasing Organizations</i>	7	3	Discounts and rebates by class of trade
Purchasers	58	23	
<i>Independent Physician Offices</i>	36	7	Invoices for focus drugs
<i>Hospitals</i>	7	12	Invoices for focus drugs
<i>HMOs</i>	8	2	Invoices for focus drugs
<i>PBMs</i>	7	2	Invoices for focus drugs
TOTAL:	89	36	
Secondary Data			
Data	Source		Notes
Average Invoice Prices	IMS		All drugs. 11 retail and provider categories
List Prices (AWP and WAC)	MediSpan		All drugs
HCPC-NDC Crosswalk	CMS		Most Part B drugs

The primary data collection focused on six HCPCs: J0880 (darbepoetin alfa injection), Q0136 (epoetin alpha injection for non-ESRD use), J9202 (goserelin acetate implant), J9355 (trastuzumab injection), J9217 (leuprolide acetate suspension), and J9265 (paclitaxel injection).

2.2 Strengths and Limitations of the Research Data

In order to undertake any study, one must have access to adequate data. The ideal data set for a study of net acquisition costs would be based on a very large sample of acquisition cost data from a representative sample of purchasers. It would identify each purchaser's class of trade and each

purchaser's volume, both for the individual sale and on an annual basis; classes of trade would be defined in a manner consistent with the project's objectives. This ideal data set would include all three components of net acquisition cost: the invoice price, any special pricing terms, and any rebate amount paid to the purchaser. Such data would presumably be collected from physicians and large volume purchasers or from their various suppliers.

Similarly, the ideal data for a study of ASP would contain ASP by class of trade, again with classes of trade defined in a manner that was consistent with project objectives. Such data could only come from manufacturers.

For the components of this study that dealt with net acquisition costs, we relied on a small sample of interviews, a small sample of invoices collected directly from purchasers, and the secondary data on average invoice prices from IMS Health. The strengths of the interviews were that it offered some anecdotal information regarding special pricing terms and rebates and that it offered some context for other findings. The main limitation was that the sample size was small (36 interviews) and not necessarily representative of the population of purchasers as a whole. One cannot generalize from the interview findings; one must view them as anecdotal information. Due to time constraints, the study began with a relatively small number of target interviews. In addition, response rates for some groups were lower than expected, and we did not reach the point of saturation in the interviews, that is, we did not reach the point where we believed we had captured the full potential value of this mode of data collection.

We were also concerned that some interviews were incomplete or difficult to interpret. The interview discussed very sensitive material (prescription drug pricing), and, in many cases, respondents declined to answer questions or answered them vaguely. The interviews were also extremely complex; in a few cases, upon reviewing their notes, interviewers were concerned that they and the respondents had not fully understood each other.⁴ This was a particular concern since there were so few interviews. Finally, the fact that response rates were very low raises concerns about bias: the respondents that we did talk to may not constitute a representative sample of the underlying population.

The strengths of the primary invoice data were that it offered invoice-level data on acquisition costs and that it offered a point of comparison and confirmation for findings based on the secondary data. It also contributed a sense of the dispersion of invoice prices within a given category of purchaser.

The invoices were collected from interview respondents following the interviews. As a result, the number of invoices was small, too small to support detailed statistical analysis, and not necessarily representative. The analysis of primary price data is based on 23 invoices from six independent physician offices and 38 invoices from 12 hospitals. In addition, this data represented invoice prices only; it did not yield insight into special pricing terms or purchaser rebates.

The main data source available for analysis was the data on average invoice prices from IMS Health. The strengths of this data were that it was based on a large representative sample of all purchasers and available for the full range of Part B drugs. While very useful, this data had several important limitations, the first being that the average invoice price (AIP) differs from average net acquisition cost because AIP does not capture special pricing terms or manufacturer rebates.

Another important limitation was the fact that the AIPs were based on broad classes of trade, many of which contained different sub-categories believed to receive differential pricing. For example, the

⁴ In order to respect the respondent's privacy, Abt did not tape interviews so questionable passages could not be double-checked.

hospital category contained both teaching and community hospitals. In the experience of the project team and in the opinion of some interview respondents, these two types of hospitals paid different prices for their Part B drugs. Also, the clinic category contained physician offices, clinics, and some hospital outpatient departments, including some outpatient departments that were eligible for federally-negotiated 340B pricing. Again, the different groups within this category may well pay different prices for their Part B drugs. This is also significant since the sales of drug products to 340B program participants are exempt from the ASP calculation. As a result, the average for the broad class of trade was not equal to the average for each of the sub-categories within it.

A final limitation was that, regardless of whether average invoice prices were available for finer classes of trade, the IMS data reflected *average* prices and did not provide a measure of price dispersion within a given class of trade. Individual buyers might face prices above or below those averages, and the IMS data that the project received did not contain measures of dispersion that could be used to establish the empirical importance of this phenomenon.

For the component of the study that dealt with ASP, the only potential source of data was the primary data collection from manufacturers. Three manufacturers participated in interviews, but no manufacturer submitted complete data on ASP by class of trade for a focus drug. Again, while useful for this component of the study, AIP also differed from ASP because AIP included wholesaler and distributor mark-ups and because it did not capture purchaser or non-purchaser rebates.

There are two other issues that affect the interpretation of the results of this study. The first issue is the time period of the data. The interview and invoice data were collected in the spring of 2005, shortly after the implementation of ASP-based pricing. The IMS data contained invoices from the third quarter of 2004, prior to the ASP implementation. This study provided an analysis of the market for the drug covered by Medicare at a point in time, but this market may well change in response to the new coverage and pricing environment created by the MMA.

The second issue is that classes of trade are not well-defined. The definitions of the various types of classes are not clear and consistent among market participants; several experts explicitly noted that this was a problem. In addition, market participants' working definitions of the classes of trade are not necessarily consistent with the MMA's implied concepts of prudent physicians and large volume purchasers.

2.3 Selection of Six HCPCs for Primary Data Collection and Focused Review

The primary data collection and some analyses of secondary data were focused on six HCPCs, presented in Exhibit 2.2. These HCPCs covered drugs typically prescribed by a range of physician specialties and for several different indications (three physician specialties and three indications). The design also featured two HCPCs for each physician type and indication, so that the project team could collect more primary physician data per HCPC than would otherwise be the case. All selected HCPCs were significant in terms of Medicare expenditures.

Four of these six focus HCPCs were used to choose the four physician samples and were the primary drug on which a purchaser interview focused. These four HCPCs are referred to as anchor HCPCs in Exhibit 2.2. A purchaser interview focused on the drugs in one of the four anchor HCPCs; however, primary data were requested for each of the six focus HCPCs.

Exhibit 2.2: Six HCPCs for Primary Data Collection and Focused Review

HCPC Description and Code Percent of 2003 Part B Drug Expenditures	Physician Type & Indication	Product Names (Manufacturer)
darbepoetin alfa ** (J0880) 5.1 percent	Oncologist/hematologist Anemia associated with chemotherapy	Aranesp® (Amgen)
erythropoietin alpha (Q0136) 8.9 percent	Oncologist/hematologist Anemia associated with chemotherapy	Procrit® (Ortho)
goserelin ** (J9202) 4.3 percent	Urologist Prostatic cancer	Zoladex® (AstraZeneca)
leuprolide acetate (J9217) 6.9 percent	Urologist Prostatic cancer	Lupron® (TAP) Eligard® (Sanofi) Viadur® (Bayer) generics (Eon Labs, IVAX, Sicor)
paclitaxel ** (J9265) 2.5 percent	Oncologist Breast cancer	Taxol® (BristolMyers Squibb), Onxol® (IVAX) [branded generic], generics (AmeriNet Choice, UDL, Mayne, Bedford)
trastuzumab ** (J9355) 0.9 percent	Oncologist Breast cancer	Herceptin® (Genentech)

** These four HCPCs anchored the physician sample frame, i.e., they were used in the physician screening process.

2.4 Interviews and Primary Data Collection

Individual in-depth interviews were conducted by telephone with various groups of respondents, namely: experts, manufacturers, group purchasing organizations (GPOs), wholesalers, physicians, hospitals, HMOs⁵, and PBMs. All 36 interviews took place between April 1, 2005 and May 13, 2005. Exhibit 2.3 displays the project team's target numbers of interviews and response rates, by respondent group.

⁵ HMOs, health maintenance organizations, were found in the 2003 Healthcare Distribution Management Association (HDMA) Industry Profile and Healthcare Factbook, and were the top managed care firms by HMO enrollment.

Exhibit 2.3: Target Numbers of Interviews and Response Rates

							Response Rate	
	Target	Letters Sent	Interviews Completed	Refused	Ineligible	Passive Refusal⁶	% of Target	% of Letters
Experts	8	14	6	2		6	75%	43%
Manufacturers	9	11	3	5		3	33%	27%
GPOs	7	8	3	3	1	1	43%	38%
Wholesalers	7	20	1	3	3	13	14%	5%
Physicians	36	72	7	25	1	39	19%	10%
Hospitals	7	20	12	2		6	171%	60%
HMOs	8	18	2	2	6	8	25%	11%
PBMs	7	14	2		9	3	29%	14%
TOTAL	89	177	36	42	20	79	40%	20%

Interview procedures were designed to create an objective and accurate documentation of respondent perspectives. For each of the groups, the project team identified an objective and representative source of potential respondents and created an initial sample (Appendix B offers more details about the development of the interview samples and other methodological issues.). Unfortunately, for some groups, we had trouble reaching the target number of interviews because representatives from these organizations were unwilling to participate.

Interviews were conducted using a discussion guide. The interview guides varied for the different respondent groups, with some similar questions for all groups. The discussion guides were comprised of open-ended questions, which asked about drug acquisition processes and pricing patterns for Medicare Part B drugs, as well as specific questions pertaining to the drugs in the six focus HCPCs in our study.

At the end of the interview, all respondents except experts were asked to voluntarily submit drug pricing data. Manufacturers, wholesalers, and GPOs were asked to fill out a data collection form. In the data collection form, manufacturers were asked to provide information regarding ASP at the NDC-11 level by class of trade. Wholesalers and GPOs were asked to provide net invoice prices (relative to the so-called wholesale acquisition cost or WAC) and rebates amounts from manufacturer to purchaser at the NDC-11 level by class of trade. After the interview, the project team would customize the data collection form in light of the interview so that it reflected information gathered about relevant NDC-11s and relevant classes of trade.

Physician purchasing agents, hospitals, HMOs and PBMs were asked to submit pricing data regarding drug products in the six focus HCPCs in the form of a recent invoice. Exhibit 2.4 presents the data received.

⁶ Our definition of passive refusal was when we left at least five voice messages for a potential respondent and the person never returned our call to either agree or refuse to participate. Messages clearly stated that the study was being done on behalf of CMS.

Of eleven manufacturers contacted, three participated in interviews, but none submitted complete data on ASP by class of trade for a focus drug. Price data submitted by wholesalers, GPOs, HMOs, and PBMs was very limited and was incorporated into the analysis of interviews. Price data submitted by physicians' offices and hospitals were also limited but were analyzed separately to the extent possible. Most of the invoices submitted were dated March or April 2005.

Exhibit 2.4: Primary Data on Invoice Prices: Data Received

Respondent Category	N Complete Interviews	N Submitting Data Forms	Data Received (Invoices or Data Collection Forms)
Manufacturers	3	1	No complete data collection forms for focus drugs
Market Intermediaries			
<i>Wholesalers</i>	1	0	
<i>Group Purchasing Organizations</i>	3	2	2 data collection forms which included discount and rebate information
Purchasers			
<i>Independent Physician Offices</i>	7	6	23 invoices
<i>Hospitals</i>	12	12	38 invoices
<i>HMOs</i>	2	1	Some data via email
<i>PBMs</i>	2	1	8 invoices
TOTAL	30	23	

The primary data collection focused on six HCPCs: J0880 (darbepoetin alfa injection), Q0136 (epoetin alpha injection for non-ESRD use), J9202 (goserelin acetate implant), J9355 (trastuzumab injection), J9217 (leuprolide acetate suspension), and J9265 (paclitaxel injection).

All potential respondents were assured that their participation was voluntary and confidential.

2.5 Secondary Data on Drug Prices

In addition to interviews and primary invoice data, the project team conducted an analysis of secondary data on average invoice prices for the drugs covered by Medicare Part B.

Data Sources

To create a database for analysis of Medicare Part B drug prices, price data and variables related to the characteristics of specific drug products were acquired from three different secondary data sources: (1) IMS Health, Inc., (2) the Centers for Medicare and Medicaid Services (CMS) and (3) Medi-Span (a division of Wolters Kluwer Health, Inc.). Invoice drug price data was acquired from IMS Health's National Sales Perspective (NSP) database. From CMS, two files were used including: the HCPCs Crosswalk File (January 2005), and the CMS NDC Weight File. Medi-Span's PriceChek PC database was used for current drug prices and their Master Drug Data Base (MDDB) was used for archival prices and drug product characteristics.

IMS Health's National Sales Perspective Database

IMS Health's NSP database reports the total sales dollars and number of units that were distributed to purchasers for virtually all prescription drugs on a monthly basis. The data are collected by IMS from electronic and scanned invoices that are generated by manufacturers or wholesalers when drugs are sold to purchasers. As a result, estimates of average invoice price (AIP) based on this data include all on-invoice discounts, such as including bottom line discounts.

Sales data were available from IMS at the 11-digit National Drug Code (NDC-11) level. The NDC-11 level uniquely identifies the active molecule, dosage form, strength, package size, package type, and manufacturer or marketer for each and every prescription drug product on the market. IMS monthly sales and unit volume data for major Medicare Part B drug products by class of trade at the NDC-11 level for the period January 2002 through January 2005 was analyzed for this project, although this report only shows data from the third quarter of 2004 (Q3 2004).

Data related to purchasers are grouped into thirteen broad classes of trade by IMS including: independent pharmacies, chain pharmacies, food stores, mail service pharmacies, HMOs, clinics, home health care, long-term care facilities, non-federal hospitals, federal facilities and miscellaneous (including prisons, universities, and others). Clinics are defined by IMS as an individual physician or a group of physicians located at the same address, which includes oncology clinics, outpatient dialysis facilities, OB-Gyn clinics, orthopedic clinics, outpatient emergency treatment centers, multi-specialty clinics, and other types of outpatient clinics,⁷ including those that are eligible for federally-negotiated prices on drugs under the 340B program. The breadth of this clinic category is unfortunate for our study because we would like to be able to distinguish among these sub-categories of purchasers.

Data Sources from CMS

The CMS HCPCS-NDC Crosswalk file (January 2005) is publicly available file that was obtained from the CMS website.⁸ This MS Excel file contains almost all drug HCPCs and identifies the NDCs at the 11-digit level that are related to each specific HCPC. In addition to the HCPCS-NDC crosswalk, the file also contains information for each 11-digit NDC on the labeler name, drug name, package size, package quantity, billable units per package, and billable units per 11-digit NDC.

The CMS NDC Weight File was provided to the project team directly by CMS. This file contains data at the NDC-11 level for each NDC included in the calculation of the ASP for a specific HCPC. The NDC Weight Factor is a value calculated by dividing the billable units of a specific NDC-11 sold during a certain period by the total number of billable units for all NDC-11s that are included within a specific HCPC that were sold during the same time period. The CMS NDC Weight file (Third Quarter 2004) contains NDC Weight Factors for each NDC-11 based on actual sales during the third quarter of 2004.⁹ This file also contains a HCPC description and the number of billable units per package at the NDC-11 level.

Data Acquired from Medi-Span

Drug product characteristics and related background information, such as therapeutic category, patent status, and manufacturer, was acquired from the Medi-Span MDDB File. Medi-Span is a division of Wolters Kluwer Health, Inc.

⁷ DDD Outlet Subcategory Codes, IMS Health, October 2002. More details on IMS' classes of trade are in Appendix E.

⁸ The CMS HCPCS Crosswalk File file named 'HCPCSCrosswalk0105.xls' was found at the CMS website address '<http://www.cms.hhs.gov/providers/drugs/asp.asp>'.

⁹ CMS provided NDC weight factors, but not ASP prices at the NDC-11 level.

Sample Selection

A CMS analysis of Year 2003 Medicare Allowable Charges identified the top 35 HCPCs codes in terms of Medicare expenditures.¹⁰ These Top 35 HCPCs accounted for 85 percent of Medicare expenditures for Part B drugs in CY 2003 (See Appendix D). A HCPC is a grouping code for drug products (at the NDC-11 level) that have the same chemical entity and dosage form that can be used to deliver a specific amount of medication. Each unique dosage form, strength, and package size of a drug produced by each manufacturer is assigned a unique NDC-11 number. The project team chose to focus on the 25 HCPCs that were most significant in terms of 2003 Medicare expenditures and that met other project criteria, for example, vaccines, respiratory drugs, and miscellaneous categories were removed at the request of CMS. Two of the HCPCs, adenosine injection (HCPC J0151) and verteporfin injection (HCPC J3395), did not have any NDC-11s attributed to them in the third quarter 2004 weight file and were therefore removed from the analysis. Finally, Hylan G-F 20 injection (HCPC J7320) did not have any IMS data available for the only weighted NDC-11 and was also removed from analysis. The remaining 25 HCPCs were linked with 165 drug products at the NDC-11 level.¹¹ These HCPCs and their related drug products formed the analytic data set that was the focus for the analysis in this study.

Creation of the Analytic File

Data from the IMS NSP database was selected at the drug molecule level, since the IMS database does not link the drug products (NDC-11) into HCPCs groups. Sales volume (in dollars) and number of package units sold for each of the classes of trade were extracted at the NDC-11 level for each molecule that was described by one of the 25 study HCPCs.¹² Data was selected for July, August and September of 2004 which is the same time period as the ASP data submitted by manufacturers to CMS for calculating the third quarter 2004 ASP that will be applied as a payment limit in the first quarter of 2005. The IMS NSP data was extracted and exported from the IMS' Dataview database into MS Excel. Stata version 8.0 was used to perform calculations with this data set such as calculation of price per billable unit for each NDC-11 and to conduct price analysis for various groupings of NDC-11s or classes of trade.

The IMS NSP data was matched by NDC-11 number to the data found in the CMS HCPCS-NDC Crosswalk and the CMS NDC Weight File to map each NDC-11 into one of the 25 study HCPCs. The IMS NSP sales and package units data were used at the NDC-11 level to calculate a price per package unit. Price per dose was then calculated for each NDC-11 by dividing the IMS price per package unit by the Billable Units Per NDC-11 provided in the CMS NDC Weight File.

Construction of Analytic Variables and Analytic Methods

The final analytic file created in Stata contained an average invoice price per dose (AIP) for each class of trade for each of the NDC-11s that comprise the 25 study HCPCs for each month across the time period January 2002 to December 2004. For each NDC-11 and each class of trade, the project team created a weight (the IMS class-specific weight) that reflected that NDC-11's share of doses within the HCPC (defined in terms of the set of NDC-11s that the CMS NDC weight file associated

¹⁰ This report on CMS Year 2003 Medicare Allowable Charges was provided by CMS.

¹¹ According to the third quarter 2004 CMS NDC Weight File.

¹² Units are defined for each NDC-11 in the IMS NSP database as number of packages (equivalent to a stock keeping unit, e.g., 4 vials of 10 ml each constitute one unit), extended units (equivalent to total package quantity, e.g., 4 vials of 10 ml each constitute 40 ml of extended units) and eaches (equivalent to package quantity, e.g., 4 vials of 10 ml each constitute 4 eaches). In our analysis, IMS units are used.

with the HCPCs). The price per dose was then multiplied by the IMS class specific weight and then summed across a whole HCPC to calculate an AIP for the class of trade. AIPs based on these class-specific weights were calculated for each class of trade and for the total market (all classes of trade combined excluding federal facilities). The project team also calculated and analyzed AIPs using the CMS weights, but these analyses are not shown in the report to maintain ASP data confidentiality.¹³

Invoice prices at the HCPC level may vary by class of trade for two or more reasons. First, purchasers in different classes of trade may pay a different invoice price when purchasing the same NDC-11 drug product from a manufacturer or wholesaler. This first source of variation in invoice prices by class of trade can be isolated by analyzing an alternate AIP that is defined using standardized weights. This method assumes that each class of trade purchases the same mix from the basket of NDC-11s within a HCPC, so that any variation in the alternate AIP that is observed can be attributed solely to variations in price of specific NDC-11s. For this purpose, we constructed an alternate AIP, using weights based on combined volumes for all classes in the IMS data.

Second, purchasers in different classes of trade may acquire different drug products (with different NDC-11s) to deliver the amount of a medication specified by a certain HCPC. To analyze this second source of variation, one can compare the result obtained with the class-specific weights to the result obtained with the all-class weights.

3.0 Results: Interviews

The project team interviewed 36 experts and market participants. Appendix C offers a brief description of the interview respondents.

3.1 Distribution Process

Major Purchaser Types

Interview respondents agreed that the major purchasers of Part B drugs were physicians and hospitals, not GPOs, HMOs or PBMs. The role of GPOs is to negotiate contracts on behalf of purchasers but not to take possession of drugs.

Some HMOs, namely those with staff physicians or who own and operate pharmacies, buy through wholesalers at contract prices. The majority of HMOs, however, are primarily a financial umbrella and may never directly purchase or handle drug products. While eight HMOs initially agreed to be interviewed for this project, only two purchased drugs and qualified for the study. This is direct evidence that most HMOs do not acquire the drugs covered by Part B.

Similarly, the traditional function of the PBM is to negotiate prices between providers and insurers and contract with networks of retail pharmacies, but not to take physical possession of drug products. PBMs with mail order houses or specialty pharmacies may directly purchase and take possession of drug products for distribution through these specialized delivery channels¹⁴. There are also specialty PBMs who focus only on high cost and limited use drug products (such as Medicare Part B covered drugs). While eleven PBMs initially agreed to be interviewed for this project, only two purchased

¹³ To make the IMS all-class-weighted AIP and the CMS -weighted AIP comparable to the Average Sales Price, sales to federal facilities were excluded from the AIPs that were calculated for the total market with all classes of trade combined.

¹⁴ Most of the largest PBMs do own their own mail service pharmacy.

drugs and therefore qualified for this study. Again, this shows that most PBMs do not acquire Part B drugs.

Channels of Distribution

There was consensus in the interviews that physicians often purchased drugs from specialty distributors, specialty wholesalers, or specialty divisions within major wholesalers while hospitals typically purchased via major wholesalers. The view that physicians and hospitals work with different distribution channels was confirmed by respondents' description of their own distribution and acquisition practices. While the use of different distribution channels is not evidence of differences in net acquisition costs, it may facilitate the persistence of such differences.

In response to questions about distribution channels, each manufacturer reported a different approach to distributing the product under discussion. Two firms shipped to physicians via one or more specialty distributors. The third manufacturer distributed its drug products to physicians through major wholesalers using a charge-back system. In a charge-back system, a wholesaler acquires a drug from a manufacturer at WAC (wholesale acquisition cost, a list price not necessarily reflecting actual acquisition costs), or some other list price. The wholesaler then sells the drug at a different price, often below WAC or the other list price, and then charges the difference back to the manufacturer. All three manufacturers distributed to the hospital class of trade using major wholesalers and charge-backs.

All physicians reported that their clinics purchased most of their drugs from specialty distributors or specialty wholesalers, while every hospital purchased drugs through at least one of the big three wholesalers (McKesson, AmeriSource-Bergen, or Cardinal).

In hospitals, some respondents indicated that they also negotiated directly with manufacturers for price and discounts on certain drugs. This practice was more common among the academic medical centers and large multi-hospital systems than it was for community hospitals. Some of these academic centers suggested that they were able to obtain better direct discounts from manufacturers for a variety of reasons including: size, prestige in a given specialty (e.g., oncology, cardiology, orthopedics, etc.), and ability to influence young physicians' choices with regard to particular drugs.

Both HMOs and both PBMs worked with a major wholesaler (not necessarily the same wholesaler).

3.2 Access to Special Pricing Terms and Rebates

Access to Special Pricing Terms

In conversations with purchasers, interviewers inquired about the purchasers' access to special pricing terms from wholesalers and access to rebates. Manufacturers were also invited to comment on rebates. We found that there were two basic types of discounts from wholesalers or distributors – prompt pay discounts and volume or prime vendor discounts.

Prompt Pay Discounts

Prompt pay discounts were discounts for the timely payment of an invoice that reduced actual acquisition costs below the amount listed on the invoice. Purchasers' comments offered anecdotal evidence that physicians might derive less benefit from prompt pay discounts than hospitals.

Each of the physician respondents indicated that a prompt-pay discount was available if they paid for drugs within a certain time frame. The level of the discount ranged from one to two and one-half percent. One of the two clinics that reported having a two and one-half percent discount had their

drug payments directly deducted from their bank account. The other clinic had to pay their invoice within one week in order to receive its discount.

Respondents from two of the clinics reported that their clinic almost always received its prompt-pay discounts. It was unclear whether four of the respondents were able to receive the prompt-pay discount every time they purchased drugs. One office was unable to take advantage of its one percent prompt pay discount. Paying its invoices immediately would require that this respondent secure and pay the finance charges on a one million dollar line of credit. Since commercial payers and Medicare generally do not pay this clinic for 45-60 days¹⁵, the clinic was unable to pay their drug invoices immediately.

All hospital respondents reported prompt-pay discounts from their wholesalers, and a few even received a discount for pre-paying drug costs.

One of the two HMOs received prompt-pay discounts; the other did not comment. Both PBMs received these discounts.

Volume Discounts

Wholesaler volume discounts are usually based on two criteria – the total dollar volume of all drugs purchased over time from the same wholesaler and/or the total share of an end purchaser's volume that is purchased from the wholesaler serving as their 'prime vendor.' Like manufacturer rebates, they are paid after-the-fact and do not appear on invoices.

Again, the interviews offered anecdotal evidence that hospitals enjoyed better access to such discounts than physicians. Only two respondents in physicians' offices indicated that they received volume discounts on the drugs they purchased. Every hospital reported that purchase volume influenced their discounts, both from wholesalers and from manufacturers from whom drugs were directly purchased. Manufacturer-based volume discounts are usually limited to purchases of a specific drug, or sometimes a bundle of specific drugs, from the manufacturer within a certain time period.

Both PBMs negotiated for wholesaler discounts based on volume.

Access to Rebates

When asked to discuss rebates, one manufacturer described them as "performance rewards to end customers," recognizing sales, growth in sales, market share, and growth in market share. Rebates are typically administered after-the-fact based on performance over some period of time; they are typically paid directly by the manufacturer to the provider. "Market share rebates" reward the use of one drug in a competitive therapeutic class at a particular level; for example, given a choice of two drugs for a condition, a provider might receive a rebate if one of the drugs was used in 80 or 85 percent of cases. "Market basket rebates" recognize a provider's use of a set of several drugs from the same manufacturer and are paid if the total use of these drugs surpasses a certain market share. No manufacturer was willing to discuss the magnitude of rebates.

The interviews suggested that physicians might have been disadvantaged relative to hospitals in terms of access to manufacturer rebates. Manufacturer rebates were not common at any of the physician clinics interviewed. The respondents who did report such rebates indicated that they were only available for a small number of drugs (generally less than five). Two respondents reported that the

¹⁵ It is likely that this respondent relied on a paper process to bill Medicare. Medicare pays electronic claims within 30 days of receipt.

manufacturer rebates their clinics received were tied to either volume or market share. One respondent suggested that rebates were only available on brand name drugs, never on generic drugs. Respondents at one manufacturer emphasized that, for their product, non-purchaser rebates were important.

Each hospital received some direct manufacturer rebates, typically amounting to about one to two percent of their annual purchase volume. At the larger institutions, where total purchases may exceed \$100 million, this represented a significant amount. Many hospitals claimed that they were trying to migrate away from rebates, since they are always *post hoc*, and hence are difficult to incorporate rationally into their financial management and purchase planning. Some multi-hospital systems also mentioned that rebates were difficult to allocate among members.

Both HMOs surveyed received manufacturer rebates on certain drugs based upon formulary placement, volume, market-share, and market-basket performance, but neither received rebates for any of the four anchor Medicare Part B drugs discussed in detail.

The two PBMs that were interviewed had formularies and they each received rebates both for placement of drugs on the formulary and for driving market share movement (increasing the percent of prescriptions in a certain therapeutic class for a specific drug product). Both PBMs also received direct volume discounts from manufacturers, independent of their wholesaler arrangements. One PBM also indicated that it received fees from some manufacturers for administering the rebates that these manufacturers paid directly to the PBM's customers.

3.3 Variation in Net Acquisition Costs

Existence of Variation

When asked whether prices varied across different classes of purchasers, one respondent replied "Absolutely." There was widespread agreement among all groups of interview respondents, other than manufacturers, that net acquisition costs varied for different types of purchasers.

Manufacturers were circumspect on this point. Respondents at one manufacturer could not comment on this question; they noted that, because they worked with a distributor, they did not know what prices physicians ultimately paid to acquire their product; that was at the distributor's discretion. Respondents at the second stated that the pricing distributions for different classes of trade overlapped (contracts were based on size and performance attributes as opposed to class of trade), but that generally smaller customers and the retail class of trade paid more. The third said, without reservation, that physicians and hospitals were eligible for the very same discounts.

Interviewers inquired whether differences in net acquisition costs were due to different purchasers paying different prices for the same drug or whether they were due to different purchasers choosing different drugs (NDC-11s) within a given molecule. Referring the specific drug under discussion, these three manufacturers stated that, to the extent difference in net acquisition costs existed, they stemmed from purchasers buying the same drug product (at the NDC-11 level) at different prices; there were not important differences in which classes of trade acquired different products within a molecule. A few physicians noted that small purchasers might also buy different NDC-11s (e.g., smaller package sizes with fewer doses) within a given molecule, because they needed fewer doses over time.

Interviewers also asked about the role of wholesaler or distributor mark-ups in determining net acquisition costs and variation in net acquisition cost. Interview respondents agreed that pricing decisions made at the manufacturer level were the drivers of variation in acquisition costs and that

wholesalers' and distributors' mark-ups were much less important. No respondent emphasized that wholesaler or distributor mark-ups were large; in fact, some emphasized that they were small. No respondent emphasized that these mark-ups varied by class of trade, although, as just noted, there was some evidence of variation in purchasers' access to special pricing terms from their wholesaler or distributor. While wholesalers and GPOs facilitate drug distribution and price negotiation, all four of these respondents (three GPOs and one wholesaler) were adamant that it is manufacturers who effectively set prices for all brand name drugs.

The implication of this perception is that differences in net acquisition costs would likely be reflected in ASP if it were calculated by class of trade. As noted earlier, one manufacturer emphasized that, for their product, non-purchaser rebates were important.

Drivers of Variation

Respondents cited several interacting drivers of the variation in acquisition costs. Some of these drivers pertained to purchaser characteristics and others to drug product characteristics.

Purchaser Characteristics

Class of trade, such as physician, hospital, or retail pharmacy: Several experts and all intermediaries cited class of trade itself as a driver of differences in pricing.¹⁶ As noted above, both respondents at PBMs (who had both formerly been in specialty pharmacies) noted that their net acquisition costs had risen with the change in class of trade.

Ability to influence market share directly: Five of the six experts and all of the intermediaries volunteered that the ability to influence market share was a key driver of differences in acquisition costs. Some purchasers, such as PBMs or HMOs with salaried physicians, are able to affect utilization because they establish a formulary or a preferred drug list that influences prescribers' choices. Perceived status may also create influence; a prominent teaching hospital sets lifelong prescribing patterns for young physicians and influences physicians in the surrounding community. Purchasers with the ability to influence market share are typically compensated after the fact via rebates. Experts indicated that some classes of trade, notably retail pharmacies, typically are ineligible for (or are not offered) market share rebates from brand manufacturers.

Volume: Five of the six experts and three of the four intermediaries stated clearly that volume was a driver of discounts and rebates especially within, as well as sometimes between, classes of trade.

Purchaser expertise: Two respondents pointed out that the market for prescription drugs is very complicated and that more sophisticated purchasers were in a better position to navigate that market and secure the lowest prices.

Drug Characteristics

Therapeutic competition: According to several respondents, unique (patent protected) products are sold at list price (WAC) with little variation. Once a manufacturer is forced to compete for market share against a therapeutic alternative, then the manufacturer may begin to provide discounts and rebates and to do so selectively.

¹⁶ The implications of class of trade pricing are described in more detail in a CMS report, Schondelmeyer SW and MV Wrobel, Medicaid and Medicare Drug Pricing: Strategy to Determine Market Prices, Final Report, Contract #500-00-0049, Task Order 1, August 30, 2004. See pages 16 to 19 and other sections.

Generic competition: Similarly, generic competition drives down the price of prescription drugs. Two respondents stated that because the market for generic drugs is so competitive, all purchasers have access to excellent pricing. While generic competition eliminates monopoly-pricing power, it does not necessarily equalize prices among purchasers in different classes of trade. The ability to influence which manufacturer's drug product is used, when multiple generic drug products are available, often leads to a lower price.

Whether the drug is an oncology drug: Two respondents suggested that markets for oncology drugs are different than the markets for other pharmaceutical products. First, as one respondent noted, oncologists received greater discounts than other physicians. Also, as another respondent noted, unlike most physicians, it is to oncologists' advantage to work with specialty distributors rather than major wholesalers. Large networks of oncologists existed to serve as an "oncology GPO" or a specialty distributor.

Other Characteristics

Competition among suppliers: Two experts noted that specialty wholesalers and distributors would try to match market prices for particular drugs.

Ranking of Purchaser Types

When asked to rank which classes of trade faced higher net acquisition costs, interviews with four experts suggested that physicians pay more than hospitals while interviews with 2 GPOs and 1 expert suggested a mixed picture across drugs.

Experts were asked to discuss general patterns among all of the drugs covered by Part B of Medicare. In this context, four of the experts clearly stated that physicians faced higher net acquisition costs than hospitals; one stated that results were mixed.

Respondents at GPOs were asked to discuss each of the six focus drugs and provide associated price data. Respondents from two of the three GPOs were willing to discuss discounts and rebates in the interview and to submit data collection forms. Both of these respondents agreed that (1) for two of the six focus drugs physicians and hospitals faced similar net acquisition costs; (2) for two of the six focus drugs, physicians faced higher net acquisition costs than hospitals. In the latter case, both differential invoice prices and differential rebates contributed to the total net difference. There was not a clear consensus regarding the remaining two focus drugs.

The belief among some interview respondents that physicians paid more than hospitals is noteworthy because it differs from the findings on invoice prices in the secondary data analysis. This underscores the need for data on off-invoice price concessions to determine how net acquisition costs compare across provider types.

4.0 Results: Secondary Data Analysis

This chapter discusses results of an analysis of secondary drug price data for the 25 study HCPCs. As emphasized in the methods chapter, it is important to remember the limitations of this data. First, the average invoice price (AIP) was different from the average net acquisition cost because it did not capture special pricing terms or manufacturer rebates. Second, the volumes and average invoice prices presented below were calculated for broad classes of trade, many of which contained different sub-categories believed to receive differential pricing. For example, the "clinic" category contained

physician offices, clinics, and some hospital outpatient departments, including some hospital outpatient departments that were eligible for federally-negotiated 340B pricing.

4.1 Major Purchasers

The 25 study HCPCs and related drug products accounted for nearly two-thirds (63 percent) of the Medicare Part B drug expenditures in 2003. The share of doses (Exhibit 4.1) and the share of dollars (Exhibit 4.2) for drug products in each of the 25 study HCPCs was examined for each of the classes of trade.

Clinics or hospitals were the primary purchasers of doses in 22 of the 25 study HCPCs during the third quarter of 2004 (Exhibit 4.1). In addition, sales were typically split between the clinic and the hospital classes of trade. For 20 of the 25 drugs, both the clinic and the hospitals classes of trade each had at least ten percent of total sales.

The retail classes of trade were the primary purchasers of drug products in two of the three remaining HCPCs. Federal facilities were the primary purchaser of drug products in the third remaining HCPC code. Mail service pharmacies, HMOs, home health care and long term care facilities were never primary purchasers for any of these 25 drugs. The following discussion classifies the 25 HCPCs into four groups based on the primary purchaser of doses for the drug products in the HCPC.

Clinics as Primary Purchasers

Clinics were the primary purchasers for 17 of the 25 study HCPCs, purchasing over one-half of the doses for these drugs. For all but two of these 17 HCPCs, hospitals accounted for the second largest share of drug purchases with shares ranging from nine percent to 41 percent of all doses. Combined, clinics and hospitals purchased between 62 and 97 percent of the doses for drug products in these 17 HCPCs. The retail classes of trade accounted for a fairly small proportion of doses in the 17 HCPCs with drug purchases predominantly through clinics. Thirteen of these 17 HCPCs had less than two percent of all doses sold through the retail classes of trade.

All 17 of the HCPCs provided to patients primarily through outpatient clinics or physicians' offices were injectible drug products. Fifteen of the 17 HCPCs, and related drug products, primarily administered in clinics or physicians' offices were for treatment of various forms of cancer or symptoms related to chemotherapy. Eleven of these HCPCs were chemotherapy, while four were for treating symptoms of chemotherapy such as anemia or nausea and vomiting. The other two HCPCs administered most often by physicians in their office or a clinic were for arthritis or other inflammatory problems [(J1745) infliximab and (J7317) sodium hyaluronate injection].

Hospitals as Primary Purchasers

Hospitals purchased the largest share of doses in five of the 25 study HCPCs and for two of these HCPCs hospitals accounted for over one-half of the doses. Clinics were also major purchasers of drug products in these five HCPCs, purchasing between 11 and 45 percent of all doses. These two classes of trade (i.e., hospitals and clinics) purchased between 62 and 90 percent of all doses of these five HCPCs. For one HCPC, hospitals and clinics sold a nearly equal proportion of doses with 46 percent to hospitals and 45 percent to clinics.

Four of the five HCPCs that were sold predominately through hospitals were blood products including drugs for support of transplant, or other immuno-suppressed, patients and factor VIII for treatment of hemophiliac patients. The fifth HCPC sold mostly through hospitals was botulinum toxin A used for muscle paralysis, spasm control, and for other purposes.

The retail classes of trade did not purchase a substantial volume of doses for drug products in three of these HCPCs (less than two percent), but did purchase seven and 16 percent for the other two HCPCs. Home health care providers did purchase a sizeable proportion for two of these HCPCs (16 and 21 percent). These two HCPCs were also the only HCPCs where home health care providers purchased more than four percent of the total drug doses.

Retail Classes of Trade as Primary Purchasers

The retail classes of trade generally purchased a low proportion of the doses for most of the study HCPCs (less than two percent for 16 of the HCPCs and less than 17 percent for 23 of the HCPCs). However, retail pharmacies did purchase the majority of doses for drug products in two of the HCPCs: mycophenolate mofetil, oral (J7517), and tacrolimus, oral (J7507). Notably, these are the only two HCPCs among the 25 study HCPCs that are for non-injectible dosage forms of drugs (i.e., they are both oral medications). Mail service pharmacies also purchased a substantial share of the doses for mycophenolate mofetil, oral (J7517) and tacrolimus, oral (J7507). Clinics purchased less than seven percent of the doses for each of these two HCPCs for oral medication, while hospitals purchased less than four percent of the doses.

Federal Facilities as Primary Purchasers

Finally, the drugs in one study HCPC had 41 percent of all doses flow through federal facilities with the remainder of the doses divided primarily among hospitals (27 percent), clinics (21 percent), and mail service pharmacies (7 percent). The HCPC (J9219) was for leuprolide acetate implant, which is used primarily for prostate cancer. The treatment of prostate cancer in Veterans Administration hospitals would explain the high percentage of doses purchased for federal facilities.

Other Purchasers

HMOs did not purchase a substantial proportion of doses for any of the 25 HCPCs and purchased more than one percent of all doses for only two HCPCs. This class of trade purchased less than one-half of one percent of all doses for the remaining 23 study HCPCs. The IMS data did not include PBMs as a class of trade, and, as discussed earlier, pharmacy benefit managers (PBMs), in general, do not purchase drug products directly from manufacturers or wholesalers.

Mail service pharmacies, home health care facilities, and long term care facilities were not the primary purchasers of drug products in any of the 25 study HCPCs. Mail service pharmacies purchased less than two percent of all doses for 12 of the 25 study HCPCs and they purchased between two and 29 percent of the doses for the remaining 13 HCPCs. Home health care facilities purchased less than two percent of the doses for 19 of the 25 study HCPCs, and they purchased between two and 21 percent of the doses for the six remaining HCPCs. Long term care facilities purchased less than two percent of all doses for 22 of the 25 study HCPCs and they purchased between two and four percent of the doses for the remaining three HCPCs.

Exhibit 4.1: Share of Doses Purchased by Class of Trade, 25 study HCPCs, Third Quarter 2004

HCPC Code	HCPC Description	Leading Brand Name	Patent Status	Classes of Trade											
				Retail				Mail Service	HMOs	Clinics	HHC	LTC	Hospitals	Federal Facilities	Other
				Independ- dent	Chain	Food Stores	All Retail								
J0585	Botulinum toxin a per unit	Botox	SS	3%	3%	1%	7%	21%	0%	14%	1%	1%	48%	8%	0%
J0880	Darbepoetin alfa injection	Aranesp	SS	2%	3%	1%	5%	3%	0%	62%	1%	3%	24%	3%	0%
J1260	Dolasetron mesylate	Anzemet	SS	0%	0%	0%	1%	0%	0%	56%	1%	0%	41%	0%	0%
J1441	Filgrastim 480 mcg injection	Neupogen	SS	5%	9%	2%	16%	5%	0%	26%	4%	2%	43%	4%	1%
J1563	IV immune globulin	Multiple Brands	IMS/NMS	0%	0%	0%	0%	2%	0%	11%	21%	0%	62%	3%	0%
J1626	Granisetron HCl injection	Kytril	SS	0%	0%	0%	1%	1%	0%	63%	2%	0%	32%	1%	0%
J1745	Infliximab injection	Remicade	SS	1%	0%	0%	1%	3%	0%	64%	4%	0%	26%	1%	0%
J2430	Pamidronate disodium /30 MG	Pamidronate Disod	IMS/NMS	1%	0%	0%	1%	1%	0%	74%	1%	1%	19%	4%	0%
J2792	Rho (D) immune globulin h, sd	Winrho SDF	SS/NMS	1%	1%	0%	2%	1%	0%	45%	3%	0%	46%	2%	1%
J3487	Zoledronic acid	Zometa	SS	1%	0%	0%	1%	1%	0%	68%	1%	0%	26%	2%	0%
J7192	Factor viii recombinant	Helixate FS	SS	1%	0%	0%	1%	14%	0%	13%	16%	0%	55%	0%	0%
J7317	Sodium hyaluronate injection	Hyalgan	IMS/NMS	2%	4%	1%	7%	11%	0%	70%	1%	0%	7%	4%	0%
J7507	Tacrolimus oral per 1 MG	Prograf	SS	14%	34%	6%	54%	28%	0%	7%	1%	4%	4%	2%	0%
J7517	Mycophenolate mofetil oral	Cellcept	SS	14%	35%	7%	56%	29%	0%	6%	1%	3%	3%	2%	0%
J9045	Carboplatin injection	Paraplatin	SS	1%	0%	0%	1%	1%	0%	62%	1%	0%	32%	3%	0%
J9170	Docetaxel	Taxotere	SS	1%	0%	0%	1%	1%	0%	71%	1%	0%	23%	2%	0%
J9201	Gemcitabine HCl	Gemzar	SS	1%	0%	0%	1%	1%	0%	70%	1%	0%	26%	2%	0%
J9202	Goserelin acetate implant	Zoladex	SS	1%	1%	0%	2%	4%	0%	54%	0%	0%	8%	32%	0%
J9206	Irinotecan injection	Camptosar	SS	1%	0%	0%	1%	1%	2%	65%	1%	0%	27%	2%	0%
J9217	Leuprolide acetate suspension	Lupron/Eligard	SS/NMS	2%	2%	0%	4%	3%	2%	79%	1%	1%	9%	1%	0%
J9219	Leuprolide acetate implant	Viadur	SS/IMS/NMS	0%	0%	0%	1%	7%	0%	20%	1%	1%	27%	41%	1%
J9265	Paclitaxel injection	Paclitaxel	IMS/NMS	1%	0%	0%	1%	1%	0%	70%	1%	0%	24%	2%	0%
J9310	Rituximab cancer treatment	Rituxan	SS	1%	0%	0%	1%	1%	0%	65%	1%	0%	30%	3%	0%
J9355	Trastuzumab	Herceptin	SS	1%	0%	0%	1%	1%	0%	54%	2%	0%	40%	1%	0%
Q0136	Non esrd epoetin alpha inj	Procrit	Co-SS	3%	6%	1%	10%	8%	0%	53%	1%	4%	21%	2%	0%
Class of trade share of doses of all HCPCs combined				7%	15%	3%	25%	14%	0%	37%	1%	3%	17%	2%	0%

Source: IMS National Sales Perspective Database, Third Quarter 2004; CMS; MediSpan

Notes:

Patent Status codes are as follows: SS = single source drug products; Co-SS = co-licensed or co-marketed; IMS = innovator multisource drug products; NMS = non-innovator multisource (generics)

HHCs are Home Health Care facilities and LTCs are Long Term Care facilities

Share of doses by class of trade were calculated by dividing the sum all of the doses sold to that channel in the third quarter of 2004 by the sum of all doses sold to all classes of trade

Exhibit 4.2: Share of Dollars by Class of Trade, 25 study HCPCs, Third Quarter 2004

HCPC Code	HCPC Description	Leading Brand Name	Patent Status	Classes of Trade											
				Retail				Mail Service	HMOs	Clinics	HHC	LTC	Hospitals	Federal Facilities	Other
				Independent	Chain	Food Stores	All Retail								
J0585	Botulinum toxin a per unit	Botox	SS	3%	4%	1%	8%	21%	0%	12%	2%	1%	51%	5%	0%
J0880	Darbepoetin alfa injection	Aranesp	SS	2%	3%	1%	6%	3%	0%	64%	1%	4%	20%	2%	0%
J1260	Dolasetron mesylate	Anzemet	SS	0%	0%	0%	1%	0%	0%	46%	1%	0%	52%	0%	0%
J1441	Filgrastim 480 mcg injection	Neupogen	SS	6%	11%	2%	19%	5%	0%	25%	4%	2%	43%	3%	1%
J1563	IV immune globulin	Multiple brands	IMS/NMS	0%	0%	0%	0%	2%	0%	12%	23%	0%	60%	2%	0%
J1626	Granisetron HCl injection	Kytril	SS	1%	0%	0%	1%	2%	0%	58%	4%	1%	34%	0%	0%
J1745	Infliximab injection	Remicade	SS	1%	0%	0%	1%	3%	0%	64%	4%	0%	26%	1%	0%
J2430	Pamidronate disodium /30 MG	Pamidronate Disod	IMS/NMS	1%	1%	0%	2%	1%	0%	70%	2%	1%	20%	3%	0%
J2792	Rho (D) immune globulin h, sd	Winrho SDF	SS/NMS	1%	1%	0%	2%	1%	0%	44%	3%	0%	47%	2%	1%
J3487	Zoledronic acid	Zometa	SS	1%	0%	0%	1%	2%	0%	68%	1%	0%	27%	2%	0%
J7192	Factor viii recombinant	Helixate FS	SS	0%	0%	0%	0%	13%	0%	11%	16%	0%	58%	1%	0%
J7317	Sodium hyaluronate injection	Hyalgan	IMS/NMS	2%	4%	1%	7%	11%	0%	71%	1%	0%	7%	3%	0%
J7507	Tacrolimus oral per 1 MG	Prograf	SS	15%	35%	7%	57%	28%	0%	6%	1%	4%	4%	1%	0%
J7517	Mycophenolate mofetil oral	Cellcept	SS	14%	37%	7%	58%	28%	0%	5%	1%	3%	3%	1%	0%
J9045	Carboplatin injection	Paraplatin	SS	1%	0%	0%	1%	1%	0%	59%	1%	0%	35%	2%	0%
J9170	Docetaxel	Taxotere	SS	1%	0%	0%	1%	1%	0%	70%	1%	0%	24%	1%	0%
J9201	Gemcitabine HCl	Gemzar	SS	1%	0%	0%	1%	1%	0%	70%	1%	0%	26%	1%	0%
J9202	Goserelin acetate implant	Zoladex	SS	1%	2%	0%	4%	4%	0%	62%	0%	1%	11%	18%	0%
J9206	Irinotecan injection	Camptosar	SS	1%	0%	0%	1%	1%	2%	65%	1%	0%	27%	2%	0%
J9217	Leuprolide acetate suspension	Lupron/Eligard	SS/NMS	3%	4%	1%	9%	8%	2%	63%	2%	3%	13%	1%	0%
J9219	Leuprolide acetate implant	Viadur	SS/IMS/NMS	1%	1%	0%	2%	14%	0%	23%	3%	1%	30%	24%	1%
J9265	Paclitaxel injection	Paclitaxel	IMS/NMS	1%	0%	0%	2%	2%	1%	65%	2%	1%	27%	1%	0%
J9310	Rituximab cancer treatment	Rituxan	SS	1%	0%	0%	1%	1%	0%	66%	1%	0%	30%	2%	0%
J9355	Trastuzumab	Herceptin	SS	1%	0%	0%	1%	1%	0%	54%	2%	0%	41%	1%	0%
Q0136	Non esrd epoetin alpha inj	Procrit	Co-SS	6%	7%	2%	15%	7%	0%	43%	2%	7%	25%	2%	0%
Class of trade share of sales volume of all HCPCs combined				3%	3%	1%	6%	4%	0%	60%	2%	2%	24%	1%	0%

Source: IMS National Sales Perspective Database, Third Quarter 2004; CMS; MediSpan

Notes:

Patent Status codes are as follows: SS = single source drug products; Co-SS = co-licensed or co-marketed; IMS = innovator multi-source drug products; NMS = non-innovator multi-source (generics)

HHCs are Home Health Care facilities and LTCs are Long Term Care facilities

4.2 Average Invoice Prices

Variation in Average Invoice Prices per dose (AIP) by Class of Trade

AIP varied considerably among the three major classes of trade purchasing Part B drugs: clinics, hospitals, and the retail classes of trade (Exhibit 4.3).¹⁷ As a general rule, clinics (and physicians) paid the lowest AIP per dose for most of the study HCPCs and the retail classes of trade paid the highest AIP. This finding is not consistent with the findings from the interviews that physicians faced *higher* net acquisition costs than hospitals; potential explanations will be presented in the “Summary and Discussion” chapter. Also, keep in mind that AIP and net acquisition cost are not exactly the same as previously discussed and that federal and other sales that are excluded from ASP may be reflected in AIP. The comparison of AIP across classes of trade is based on the averages and does not evaluate or measure the degree of dispersion in prices within or across classes of trade.

The retail classes of trade had the lowest AIP for only one of the 25 study HCPCs (J7192, factor viii recombinant). For 19 of the study HCPCs, clinics paid the lowest AIP, while hospitals paid the lowest AIP for five HCPCs.

Average Invoice Price per Dose (AIP) by Class of Trade Versus the All-Class AIP

An AIP for all classes of trade (less the federal facilities) was calculated to approximate the ASP calculated by CMS with sales data that manufacturers are required to provide to CMS for each NDC-11 on a quarterly basis (Exhibit 4.3). The AIP for clinics was higher than the AIP for all classes of trade in the third quarter of 2004 for five of the 25 study HCPCs. Four of these five AIPs were above the all-class AIP by two percent or less. For 20 of the 25 study HCPCs, the clinic AIP was less than the all-class AIP. Ten of these HCPCs had AIPs that were more than 10 percent below the all-class AIP; the extreme value was –27 percent.

Hospitals paid invoice prices that averaged more than the AIP for all classes for 18 of the 25 study HCPCs, although for 11 of these HCPCs the hospital AIP was no more than four percent above the all-class AIP. For the remaining six HCPCs, the average invoice price for hospitals ranged from five percent to 39 percent more than the all-class AIP.

The retail classes of trade had AIPs that were greater than the all-class AIP for 24 of the 25 study HCPCs. Most (18) of these HCPCs had AIPs that were more than five percent above the all-class average with an extreme value of 181 percent higher. Nine of the HCPCs had retail AIPs more than 20 percent above the all-class average. The retail AIP was lower than the all-class average for only one HCPC—factor viii recombinant (J7192).

¹⁷ AIPs for major purchasers are in Exhibit 4.2; AIPs for all purchasers are in Appendices F and G.

Exhibit 4.3. Average Invoice Price per Dose (AIP) by Major Purchaser Classes of Trade, 25 study HCPCs, Third Quarter 2004

HCPC Code	HCPC Description	Leading Brand Name	Patent Status	All-Class AIP (not including federal facilities)	AIP by Major Class of Trade			Variation from the All-Class AIP by Class of Trade		
					Retail	Clinic	Hospital	Retail	Clinic	Hospital
J0585	Botulinum toxin a per unit	Botox	SS	\$4.30	\$4.52	\$3.60	\$4.45	5%	-16%	3%
J0880	Darbepoetin alfa injection	Aranesp	SS	\$16.99	\$21.24	\$17.31	\$14.41	25%	2%	-15%
J1260	Dolasetron mesylate	Anzemet	SS	\$5.97	\$6.36	\$4.65	\$7.05	7%	-22%	18%
J1441	Filgrastim 480 mcg injection	Neupogen	SS	\$266.49	\$301.54	\$247.36	\$259.55	13%	-7%	-3%
J1563	IV immune globulin	Multiple brands	IMS/NMS	\$40.74	\$42.88	\$42.16	\$39.47	5%	3%	-3%
J1626	Granisetron HCl injection	Kytril	SS	\$7.29	\$15.07	\$6.36	\$7.61	107%	-13%	4%
J1745	Infliximab injection	Remicade	SS	\$51.21	\$52.04	\$51.04	\$51.46	2%	0%	0%
J2430	Pamidronate disodium /30 MG	Pamidronate Disod	IMS/NMS	\$65.79	\$157.76	\$62.84	\$67.26	140%	-4%	2%
J2792	Rho(D) immune globulin h, sd	Winrho SDF	SS/NMS	\$12.23	\$12.97	\$11.85	\$12.45	6%	-3%	2%
J3487	Zoledronic acid	Zometa	SS	\$187.69	\$199.51	\$186.37	\$189.89	6%	-1%	1%
J7192	Factor viii recombinant	Helixate FS	SS	\$831.81	\$468.45	\$742.35	\$880.16	-44%	-11%	6%
J7317	Sodium hyaluronate injection	Hyalgan	IMS/NMS	\$108.84	\$115.68	\$107.44	\$113.74	6%	-1%	5%
J7507	Tacrolimus oral per 1 MG	Prograf	SS	\$3.08	\$3.20	\$2.52	\$3.12	4%	-18%	1%
J7517	Mycophenolate mofetil oral	Cellcept	SS	\$2.39	\$2.46	\$2.10	\$2.42	3%	-12%	1%
J9045	Carboplatin injection	Paraplatin	SS	\$105.36	\$128.63	\$99.29	\$113.68	22%	-6%	8%
J9170	Docetaxel	Taxotere	SS	\$276.45	\$303.95	\$272.45	\$286.74	10%	-1%	4%
J9201	Gemcitabine HCl	Gemzar	SS	\$106.28	\$109.84	\$106.89	\$103.99	3%	1%	-2%
J9202	Goserelin acetate implant	Zoladex	SS	\$192.36	\$364.13	\$180.79	\$228.51	89%	-6%	19%
J9206	Irinotecan injection	Camptosar	SS	\$117.78	\$122.29	\$118.01	\$116.51	4%	0%	-1%
J9217	Leuprolide acetate suspension	Lupron/Eligard	SS/NMS	\$245.30	\$543.97	\$180.15	\$341.40	122%	-27%	39%
J9219	Leuprolide acetate implant	Viadur	SS/IMS/NMS	\$2,534.03	\$4,777.50	\$2,192.80	\$2,213.97	89%	-13%	-13%
J9265	Paclitaxel injection	Paclitaxel	IMS/NMS	\$20.69	\$58.20	\$18.67	\$21.51	181%	-10%	4%
J9310	Rituximab cancer treatment	Rituxan	SS	\$414.21	\$428.07	\$415.17	\$411.45	3%	0%	-1%
J9355	Trastuzumab	Herceptin	SS	\$48.84	\$53.38	\$48.30	\$49.29	9%	-1%	1%
Q0136	Non esrd epoetin alpha inj	Procrit	Co-SS	\$7.18	\$10.15	\$5.58	\$8.43	41%	-22%	17%
* The All-Class AIP was calculated using the all-class weights for each drug product in the HCPC.										
* The AIP for specific classes of trade was calculated using the class-specific weights for each drug product in the HCPC.										

Sources of Variation in AIP

The project team used the IMS data to address the question of whether the primary source of variation in net acquisition costs by class of trade was purchasers in different classes of trade paying different invoice prices for the very same drug (NDC-11) or whether purchasers in different classes of trade also acquired different drug products within a given HCPC.

As a general rule, the bulk of the variation in average invoice prices could be attributed to the former issue, but, for three of the 25 HCPCs examined, compositional differences exacerbated the pricing patterns observed within NDC-11. In these three cases (J1260, Dolasetron mesylate; J1626, Granisetron HCl injection; and J9217, leuprolide acetate suspension), the use of class-of-trade specific weights increased the difference between the class-specific AIP and the all-class AIP by at least five percentage points for at least one class of trade.

5.0 Results: Primary Data on Invoice Prices

The second part of the focused review was an examination of the primary invoice data. As previously noted, the sample sizes were small in the primary invoice data due to a combination of low target numbers of respondents and low response rates. This section of the report is based on 23 invoices from six physicians' offices and 38 invoices from 12 hospitals (a total of 61 invoices), numbers too low to support much statistical analysis.

For two drugs, the limited invoice data showed that physicians paid statistically significantly more than hospitals. For four drugs, the difference in average invoice prices between physicians and hospitals was not statistically significant. Three of the six drugs had more than five physician invoices. Based on these data, the coefficients of variation within the physician class of trades were 1 percent, 4 percent, and 6 percent for the three drugs¹⁸. Four of the six drugs had more than five hospital invoices. Based on these data, the coefficients of variation within the hospital class of trade were 2 percent, 16 percent, 18 percent, and 39 percent. These estimated coefficients of variation indicate that within-class variation existed and was substantial in some cases but do not offer precise estimates of its extent because the total numbers of invoices were small. Given the small sample sizes, these results should not be interpreted as conclusive in themselves but rather as suggestive of patterns that might be explored in a more extensive sample of invoice price data, if such data were available.

6.0 Summary and Discussion

This final chapter summarizes the findings in light of the research questions, discusses the significance and limitations of the study, and offers directions for further research.

¹⁸ The coefficient of variation measures the typical deviation in the data, expressed as a percentage of the mean. For example, if the coefficient of variation is six percent and the average invoice price is \$100, then the typical invoice prices varies from the average price by \$6, either positively (\$106) or negatively (\$94). We consider coefficients of variation in excess of five percent to be substantial.

6.1 Summary

Response Rates

The interviews and primary data collection were conducted in April and May 2005. Pricing issues appeared to be very sensitive for most participants in the Medicare Part B drug market. Consequently, response rates for our study were lower than expected. Only three of the eleven manufacturers contacted agreed to participate in interviews, and none was willing to submit ASP data by class of trade for a focus drug.

Only one of the 20 wholesalers contacted participated in an interview, and this organization's contracts with manufacturers prohibited it from disclosing its contract pricing. Three of eight group purchasing organizations (GPOs) contacted participated in interviews; two shared information on their negotiated prices. Contact with 124 purchasers (physicians, hospitals, HMOs, and PBMs) yielded 23 interviews and 69 invoices for focus drugs. These low response rates were themselves a finding. Consistent with the finding of another recent report on a similar topic, we found that "Organizations that buy or sell drugs covered by Medicare are likely to be unwilling to provide price information voluntarily."¹⁹

Significance of the Findings for the Research Questions

In this section, we restate the study questions and describe the extent to which they have been answered by the study's findings.

1. *What shares of the top drugs covered by Part B of Medicare are purchased by various types of purchasers?*

Interview and secondary data concurred that the major purchasers of the top drugs covered by Part B of Medicare were physicians and hospitals, not GPOs, HMOs, or PBMs.

The secondary data analysis did offer volumes by class of trade for the categories of purchasers defined in the IMS data. For most of the 25 study HCPCs, the class of trade with the largest share of the market was clinics (including physicians' offices); hospitals were usually the class of trade with the second largest market share. Combined, these two classes accounted for more than 50 percent of all doses given in all but three of the top 25 HCPCs studied. Retail pharmacies were the class of trade with the third largest market share, and for two of the 25 HCPCs they accounted for more than 50 percent of all doses.

2. *Do different types of purchasers face the same net acquisition costs for Part B prescription drugs?*

The study was unable to obtain data on net acquisition costs by type of purchaser. However, the interviews suggested that different types of purchasers face different net acquisition costs and the primary and secondary invoice data suggested that different purchasers face different invoice prices for the prescription drugs offered by Medicare Part B examined in this study. In interviews, experts and intermediaries were unanimous in the view that net acquisition costs varied across types of purchasers; two manufacturers equivocated, however, and one disagreed. Comments made in interviews also suggested that different types of purchasers acquired drugs through different

¹⁹ Thomas J. Hoerger and John Wittenborn "Assessment of Medicare Prescription Drug Prices," Final Report, RTI Project 07964.001 (client: CMS), July 2002.

distribution channels, a fact that may facilitate differences in net acquisition cost, and that access to special pricing terms from suppliers and to rebates differed among different types of purchasers.

The primary invoice data showed statistically significant differences in mean invoice prices between physicians and hospitals for two out of the six focus drugs. The primary data also highlighted the fact that invoice prices vary within as well as between the physician and hospital groups; coefficients of variation ranged from 1 to 39 percent. In the secondary data (IMS data), average invoice prices (AIPs) varied considerably among the major classes of trade purchasing Part B drugs.

Both comments made in interviews and a focused review of six HCPCs using secondary data indicated that the main source of variation in net acquisition costs (interviews) or AIP (secondary data) was different purchasers paying different prices for the same NDC-11, not different purchasers choosing different NDC-11s for these drugs.

The interviews also yielded a list of purchaser-level drivers of net acquisition costs, namely class of trade, ability to influence market share, volume, and purchaser expertise.

3. Which purchasers face lower and higher net acquisition costs?

While the study found that differences in net acquisition costs/invoice prices existed, we did not find conclusive and consistent evidence concerning whether physicians were disadvantaged relative to large volume purchasers. Both the interviews and the primary price data offered some anecdotal information suggesting that physicians paid higher net prices than hospitals for some drugs. Comments made in interviews suggested that physicians were at a disadvantage relative to hospitals in terms of prompt pay and volume discounts from suppliers and rebates from manufacturers. In the primary data on invoice prices, the mean invoice price for physicians was statistically significantly higher than the mean invoice price for hospitals for two of the six focus drugs. In contrast, the secondary data showed that as a general rule, clinics (the class that included physicians) faced the lowest average invoice prices per dose of all the major classes of trade for most of the study HCPCs.

This discrepancy is difficult to explain. One part of the explanation may be that the clinic class of trade in IMS Health's data is broadly defined and includes some hospital outpatient departments (including public health service and disproportionate share clinics, which are not included in the ASP calculation) so the findings for clinics may understate invoice prices for physicians. It is possible that interview respondents talked about pricing patterns over the full universe of drugs rather than specifically about the drugs covered by Part B of Medicare, despite the interviewers' efforts to focus the conversation on the latter. Finally, it is also possible that interview respondents viewed rebates as the driving force behind hospital's costs being lower than physicians, a factor which was not captured in the AIP analysis.

Both the primary data and the secondary data suggested that the retail sector faced higher net acquisition costs than the physician (or clinic) and hospital sectors.

4. If differences in net acquisition costs exist, do they vary by drug?

Both the interviews and the secondary data analysis clearly indicated that differences in net acquisition costs/average invoice prices varied by drug. The interviews highlighted that the presence of therapeutic or generic competition was a critical factor. Drugs with little to no competition (i.e., unique patent-protected drugs) rarely, if ever, were sold at a discount or rebated. Drugs with limited competition (i.e., branded, patent-protected drugs with a close therapeutic substitute) offered selective discounting and rebating to certain classes of trade. Drugs with generic competitors in the market had

substantial discounts relative to list prices for all purchaser types. Interview respondents also noted that the markets for oncology drugs were unique, even when compared with other Part B drugs.

5. *Would differences in net acquisition costs for different types of purchasers be reflected in ASP if it were calculated by class of trade?*

As a conceptual matter, ASP differs from net acquisition cost because it does not account for wholesaler and distributor mark-ups, which are part of net acquisition costs, and because it is reduced by non-purchaser rebates, which are not part of purchasers' net acquisition costs. Interview respondents suggested that wholesalers' and distributors' margins were small and that the major determinant of acquisition costs were pricing policies set at the manufacturer level and reflected in ASP. The implication of these comments is that ASP calculated by class of trade would be likely to reflect the differences in net acquisition costs by class of trade.

6. *Are there differences in ASP when it is calculated for different types of purchasers?*

The study was not conclusive on this point. No manufacturer submitted data on ASP by class of trade, and no other market participant was in a position to comment directly on this subject.

7. *Does excluding hospitals, HMOs, or other large volume purchasers affect ASP calculations?*

The study was not conclusive on this point. The effect of excluding purchasers is the product of the excluded purchasers' share of the volume and the difference in ASP between the excluded purchasers and those that remain. Because the study did not attain conclusive evidence on ASP by class of trade, the study also is unable to answer this question.

6.2 Discussion

While this study did yield interesting information, as summarized above, it was not conclusive on the key questions of whether physicians' net acquisition costs were comparable to large volume purchasers' net acquisition costs and the effect on ASP of eliminating large volume purchasers from the calculation. On the first point, findings from the interviews and the secondary data analysis were inconsistent, making it difficult to draw conclusions with confidence.

In addition, both sources of data had significant limitations. For the primary data (both interviews and invoices), the ultimate sample sizes were small, due to a combination of low target numbers of respondent and low response rates. Ultimately, the project relied on 36 interviews and invoices from six physicians' offices and twelve hospitals. One cannot generalize from the interview findings; one must view them as anecdotal and contextual information. Similarly, the sample of invoices did not support much statistical analysis. Also, some interviews were incomplete or difficult to interpret, due to the sensitivity and complexity of the material.

In both the primary and the secondary price data, the invoice price or the average invoice price (AIP) differed from the net acquisition cost or average net acquisition cost because it did not capture special pricing terms or manufacturer rebates.

Another limitation of the secondary data was that the AIPs were based on broad classes of trade, many of which contained multiple sub-categories of purchasers believed to receive differential pricing. For example, the "clinic" category contained physician offices, clinics, and some hospital outpatient departments, including those that are eligible for federally-negotiated 340B pricing and not included in the ASP calculation. Finally, the secondary price data consisted of average prices only and did not provide measures of price dispersion within classes of trade.

The study was also unable to estimate the impact of eliminating large volume purchasers from the ASP calculation. Of eleven manufacturers contacted, three participated in interviews, but none submitted data on ASP by class of trade. This lack of primary data combined with the limits of the secondary data made it impossible to draw conclusions. AIP, as measured in the secondary data, diverged from ASP because it included wholesaler and distributor mark-ups (which are not part of ASP) and because it did not capture purchaser or non-purchaser rebates (which are part of ASP as a negative number).

Two other issues affect this study. The study is based on data collected prior to or very shortly after ASP implementation: the interview and invoice data were collected in the Spring of 2005 and the IMS data draws on invoices from the third quarter of 2004. The market for the drugs covered by Part B of Medicare may well change in response to the new environment created by the MMA.

In addition, classes of trade are not well-defined. The definitions of the various types of classes are not clear and consistent among market participants, and market participants' working definitions of the classes of trade are not necessarily consistent with the MMA's implied concepts of prudent physicians and large volume purchasers.

The sensitive and confidential nature of prescription drug pricing makes this an extremely challenging topic to research. To be successful, future work on net acquisition costs and ASP for the drugs covered by Part B of Medicare requires adequate data, ideally data that overcomes some or all of the limitations described above. At this point in time, market participants are not willing to provide price data at a sufficient level of detail to permit a thorough analysis of net acquisition costs and average selling prices by class of trade.

One potential source of such data would be IMS Health, which may have the potential to calculate average invoice prices for more granular classes of trade; the experience of this project suggests that IMS would be unlikely to make such data available and the data, even if it were available, would not reflect rebates and other off-invoice price concession. A second potential source would be large-scale primary data collection from purchasers. This would require a very large number of respondents, perhaps 400 per class of trade per drug, and very significant resources; moreover, it would duplicate work that is already done by IMS, albeit not for public purposes. GPOs are a third potential source of data on net acquisition costs. Two of the eight GPOs contacted for this study had information about both invoice prices and rebates and were willing to share it, but it is not clear whether additional GPOs would participate in similar research.²⁰ Furthermore, data collected from GPOs would not reflect the full universe of purchasers. The final source of data is the manufacturers themselves, and this project's experience suggests that they would be unlikely to share data voluntarily.

In summary, this study provided an analysis, comparing net acquisition costs across purchasers for the drugs covered by Medicare Part B, that was inconclusive and subject to limitations as just described. The potential for future studies to draw conclusions about variation in net acquisition costs across purchasers and the effect of large volume purchasers on ASP would depend almost entirely on whether the substantial challenges concerning the availability of prescription drug pricing data could be overcome.

²⁰ One GPO accepted the interview but shared limited information; four declined actively or passively; and one was ineligible.

Appendix A: List of Acronyms

AMA	American Medical Association
AMCP	Academy of Managed Care Pharmacy
ASHP	American Society of Health Systems Pharmacists
ASP	Average Sales Price
AWP	Average Wholesale Price
CMS	Centers for Medicare and Medicaid Services
DAC	Distributor Acquisition Cost
DSH	Disproportionate Share Hospital
GPO	Group Purchasing Organization
HCPC	Healthcare Common Procedure Code
HDMA	Healthcare Distribution Management Association
HHC	Home Health Care Facility
HHS	(The Department of) Health and Human Services
HMO	Health Maintenance Organization
IRB	Institutional Review Board
LTC	Long Term Care Facility
LVP	Large Volume Purchasers
MCO	Managed Care Organization
MDDB	Medi-Span Master Drug Database
Mfg	Manufacturer
MMA	Medicare Prescription Drug, Improvement and Modernization Act
MMS	Medical Marketing Services
NDC	National Drug Code (NDC-11 – 11 digit NDC)
NSP	National Sales Perspectives data (from IMS Health)
OTN	Oncology Therapeutic Network
PBM	Pharmacy Benefit Manager
Phys	Physician
VHA	Veterans Health Administration
WAC	Wholesale Acquisition Cost
WS	Wholesaler

Appendix B: Interview Methods

Overview

The data acquisition plan was designed to include primary and secondary data collection. In addition, thought leaders or experts in the field were recruited to offer another perspective on the core research questions, as well as to assist us in developing our research design and interview guide.

We set our target for data collection to be:

- Nine manufacturers;
- Seven wholesalers;
- Seven group purchasing organizations;
- Thirty-six independent physicians; and
- Seven or eight of each type of LVP (i.e., hospitals, HMOs, and PBMs).

For this study, these numbers were considered sufficient to acquire an initial perspective on market issues related to ASP and the purchase patterns for covered Medicare Part B drugs.

Sample Sources and Selection Methods

Experts

An initial list of experts was developed using individuals cited in the public and policy media, professional contacts of the project team, and recommendations of CMS. Next, a snowball strategy (asking each respondent for names and qualifications of other potential respondents) generated additional names, thus identifying the most promising candidates. The final list of 14 recruited respondents was selected in a manner that would balance expertise from various types of market participants (i.e., sellers, purchasers, and other observers) with those who were expected to have the ability to speak in an informed and candid way about the purchase of Part B drugs.

Manufacturers

Our design called for interviews with nine manufacturers of Medicare Part B drugs. Eight brand name and eight generic firms manufacture the six HCPCs listed above in Exhibit 2.2. All eight brand name and three of the eight generic firms were included in our sampling frame. CMS provided the names and contact information of the individuals who are responsible for submitting ASP data to CMS on behalf of each manufacturer in our sample.

Wholesalers

Our design called for interviews with seven representatives of wholesalers or distributors. We obtained the sample of wholesalers from the 2004 Healthcare Distribution Management Association (HDMA) Directory. There were over 80 wholesalers on this list. We selected 20 wholesalers that distributed to a wide range of classes of trade, with particular focus on firms that distributed to clinics (which include physicians' offices), hospitals, and managed care facilities. The HDMA Directory also provided contact names for these wholesalers, who generally were either the President or Vice President of the firm. We mailed invitation letters to 20 wholesalers.

Group Purchasing Organizations (GPOs)

We obtained names of GPOs from the 2003 HDMA Industry Profile and Healthcare Factbook. Our design called for interviews with seven representatives of GPOs. We used public sources, such as websites, to obtain contact names for potential respondents, which generally was for the Director of Pharmacy. Since some GPOs were subsidiaries of other GPOs on our list, we did not include the subsidiary GPOs on our list. We mailed invitation letters to eight GPOs.

Physicians' Purchasing Agents

Our design called for interviews with 36 physicians' purchasing agents at independent physician offices. To obtain a sample of physicians' purchasing agents, we purchased data on 1,000 office-based physicians from Medical Marketing Services (MMS) in February of 2005. According to MMS' records, all physicians were in a group practice with less than ten total physicians. This list consisted of 750 oncologists and 250 hematologists.²¹ The list of 1,000 physicians represented physicians from six states – California, Florida, Illinois, Kentucky, Nebraska and New York, thus reflecting both the various geographic regions of the country as well as a mix of urban and rural physician offices.

To gather contact information for the appropriate physicians' purchasing agents, we used the phone numbers for physicians' offices provided by MMS and placed phone calls to a random sample of physician's offices. At that time, we confirmed that at least one physician in the office treated the ailment that one of the four anchor drugs is used for, such as breast cancer for Herceptin. We also confirmed that the office was a stand-alone physicians' clinic and not associated with a larger hospital. If the physicians' office met these conditions, we asked for the name of the person who purchases drugs on behalf of the physicians in the office. We mailed invitation letters to 72 physicians' purchasing agents.

Hospitals

To gather our list for the target goal of interviews with seven representatives of hospitals, we contacted the American Society of Health System Pharmacists (ASHP) to obtain a list of large hospitals. ASHP provided us with a list of the largest 50 hospitals in the country based on the total number of staffed beds. This list included contact information for the pharmacy directors. After removing Veterans' hospitals and state hospitals from the list, Abt mailed invitation letters to the 20 largest hospitals on the list, with no more than three hospitals from the same state.

HMOs

Our design called for interviews with eight representatives of health maintenance organizations (HMOs). The top 25 top managed care firms by HMO enrollment were found in the 2003 Healthcare Distribution Management Association (HDMA) Industry Profile and Healthcare Factbook. Abt, then, used the 2002 Interstudy list to obtain contact information for the sampled HMOs. In most cases, we selected the largest regional division. However, six of the 25 organizations were from California. To avoid over sampling from this geographic region we selected the second largest regional division of three of these organizations. We mailed invitation letters to 18 HMOs.

²¹ MMS receives this data from the American Medical Association (AMA). AMA gives MMS contact information for almost all physicians in the U.S. A physician is excluded from the list only if he or she requests being removed from all AMA mailing lists. AMA and MMS update their physician lists weekly.

PBMs

We obtained the names of the top 20 Pharmacy Benefit Managers (PBMs) by number of covered lives from the 2003 HDMA Industry Profile and Healthcare Factbook. We obtained contact information for the 20 PBMs in our sample from the Academy of Managed Care Pharmacy (AMCP). Our design called for interviews with seven representatives of PBMs and we mailed invitation letters to 14 PBMs.

Recruitment Procedures

All potential respondents were mailed an initial recruitment letter, cosigned by a senior CMS staff member and Abt's Project Director, as well as a disclosure statement. Recruitment documents were tailored for each respondent group. A member of the project staff followed up with a telephone call to answer questions about the study and to schedule an interview if the respondent was interested in participating. If the point of contact from our sample was not the correct person we followed-up to identify the appropriate person for the interview, at which time we faxed or emailed the recruitment letter and disclosure statement to the new potential respondent.

We placed numerous phone calls to all respondents until the respondent either: scheduled an interview, refused to participate, or fell into the category of 'passive refusal' when we left at least five unreturned voice messages for a potential respondent.

Discussion Guide

Abt developed an interview discussion guide in collaboration with the University of Minnesota and CMS, based on CMS' research questions. The interview guides varied for the different respondent groups with specific questions unique to a respondent group, although certain questions were asked to all respondents. The discussion guides were comprised of open-ended questions, which asked wholesalers and purchasers about the acquisition process and acquisition costs and asked manufacturers, wholesalers, and GPOs about customers and selling prices.

Abt conducted interviews with experts at the beginning of the data collection phase, which allowed the team to increase its understanding of issues and to refine the discussion guide prior to data collection with the other respondent groups.

Interview Procedures

All respondents were promised confidentiality in the report.

The interviews were designed to take 45 minutes. Most interviews with manufacturers, experts and GPOs took approximately one hour. All interviewers and note-takers participated in a one-half-day training session. This training oriented staff to the substantive issues related to the project, data collection and recording processes, and informed consent procedures. Interviewers and note-takers also participated in a second training session focused on interviewing skills, reviewing the interview guide and data collection forms, and recruitment criteria. All interviewers were carefully trained to ensure that they would maintain a neutral position throughout the interview.

Response Rates for Interviews

All interviews included in this report were conducted between April 1, 2005 and May 13, 2005. This study was designed with the goal of conducting interviews with a total of 89 individuals, including industry experts and representatives of manufacturers, wholesalers, GPOs, large volume purchasers

and physicians' offices. Unfortunately, representatives from these organizations were often unwilling to participate.

- Six of the 14 experts recruited to participate in an interview agreed to participate.
- Five of the 11 manufacturers directly refused to participate in the study and three passively refused; only three manufacturers agreed to take part in an interview.
- Thirteen (65 percent) of the 20 wholesalers in our sample were considered a passive refusal. Three more wholesalers declined to participate and three were ineligible.
- Three of the eight GPOs in our sample participated in an interview, three refused to participate, one was ineligible and one was a passive refusal.
- Out of the 72 physician purchasing agents that we included in our sample, 39 (54 percent), were considered passive refusals; in these instances, we placed five or more calls and did not receive a response. In addition, another 25 (35 percent) physician purchasing agents directly refused to participate in the study with over half of those citing the primary reason as time. These purchasing agents did not have the time to set aside to participate in a research study. Even when we attempted to shorten the interview to 20 minutes rather than 45 minutes, time was still a factor in low participation.
- Over one-half of the hospitals in our sample agreed to participate in the interview, giving us a total of 12 completed interviews.
- While almost one-half of the HMOs in our sample were in the passive refusal category, eight of the 18 did agree to participate in an interview. We only conducted two interviews with representatives of HMOs, however, because six were ineligible.
- Eleven of the 14 PBMs in our sample agreed to participate in an interview, however we only conducted 2 interviews because nine of the 11 were ineligible for the study because they did not directly buy or sell the drugs.

Primary Data on Drug Pricing

At the end of the interviews with all respondent groups, except for experts, we invited respondents to submit drug pricing data. Similar to the interview, this data collection process was completely voluntary. Manufacturers, wholesalers, and GPOs were asked to fill out a data collection form. The manufacturer data collection form requested ASP at the NDC-11 level by class of trade. The data collection forms for wholesalers and GPOs requested list prices, invoice discounts, and rebates, if applicable, at the NDC-11 level by class of trade. These forms were carefully customized in light of information received during the interview.

Physician purchasing agents, hospitals, HMOs and PBMs were asked to submit pricing data regarding drug products in the six focus HCPCs in the form of a recent invoice. At the end of an interview, we asked respondents from these groups if they would be willing to share with us a copy of a recent invoice for the purchase of one or more drug products from the six focus HCPCs. If they agreed, we gave respondents the opportunity to fax, e-mail or mail us the invoices.

Most of the invoices submitted were dated March or April 2005.

Response Rates for Primary Data

As previously mentioned, respondents were asked to provide limited drug pricing data during the interview and to provide documentation of the price (e.g., a copy of a recent invoice) or a completed data collection form. The second column in Exhibit 2.4 (N Submitting Data Forms) details the number of respondents who provided data to Abt upon completion of the interview.

No manufacturer submitted complete data on ASP by class of trade for a focus drug.

The only wholesaler respondent was unable to provide detailed pricing data either during the interview or in a data collection form. This respondent expressed that their contracts with manufacturers prohibit disclosing pricing terms. The respondent did discuss its selling price for one drug when it sold that drug at its own “wholesaler discount” as opposed to at a contract price.

Two of the three group purchasing organizations (GPOs) interviewed completed Abt’s data collection form. Neither of the GPOs disclosed the average prices paid by different types of purchasers, however, they each provided information on the level of discounts and rebates available to each class of trade for each of the six focus drugs they distributed.

Six of the seven physician purchasing agents faxed one or more invoices after completion of the interview.

All 12 of the hospitals interviewed faxed invoices for at least one of the six focus drugs. In many cases, an invoice for more than one of the study drugs was faxed.

Representatives from two HMOs and two PBMs were interviewed. One of each of these two respondents provided data both during the interview and in a follow-up data collection form.

Review of Study Procedures

The Abt Associates Institutional Review Board (IRB) reviewed and approved the study protocol, including the disclosure statement, interview discussion guides, the data collection forms, recruitment strategies and materials, and a data security plan. Respondents were not given any monetary or other compensation for participating.

Appendix C: Interview Respondents

Description of Interview Respondents

Experts: Early in the data collection, the project team interviewed six experts, defined as individuals who were very knowledgeable about pricing practices and variation in acquisition costs. In the majority of cases, these experts were also direct participants in the supply chain, but, in contrast to respondents in other categories, experts were asked about pricing in general as opposed to their own individual situation.

Manufacturers: The project team spoke with senior managers at three pharmaceutical manufacturers, each of which made at least one of the six focus drugs. In two cases, the interview focused on the focus drug; in the third, the manufacturer opted to discuss another major Part B drug that it made. In every case, more than one individual participated in the interview, which we interpret as an indication of the significance and sensitivity of the topics of average selling prices and variation in average selling prices from their point of view. All manufacturers indicated that the study drug was administered in both physicians' offices and in hospital outpatient departments and that Medicare paid for a significant share of the study drug, defined as at least 35 percent of total units sold.²²

Wholesalers: The project team conducted an interview with one major national wholesaler.

Group Purchasing Organizations (GPOs): Three GPOs were interviewed. Two of these were large national GPOs, which worked on behalf of physicians, hospitals, and clients in other sectors; the third GPO worked with hospitals exclusively.

Physicians: We interviewed seven respondents from independent physician offices who purchase drugs on behalf of their practices. Respondents were responsible for practice administration or finance. Four of the respondents were at stand-alone clinics. The three remaining respondents were affiliated with a group of clinics (ranging from three to 12 clinics) that had centralized drug purchasing. These clinics may have been affiliated with a hospital, but all drug purchasing was conducted independent of the hospital.

Hospitals: The project team spoke with representatives of twelve hospitals, which spanned the country geographically. All but one of the respondents were part of a multi-hospital system and all were not-for-profit (NFP). The responding hospitals ranged from 500 to 1,400 beds. Several were academic medical centers, which represent a distinct class of trade from traditional community hospitals. Two hospitals were 340B-eligible, and hence purchased their Medicare Part B drugs at prices that are exempt from the ASP calculation. We discussed their inpatient purchases instead.

HMOs: Eight representatives of HMOs agreed to participate in interviews; however, only two of the eight HMOs actually purchased drugs directly and were able to complete an interview. Both HMO interviews were with the HMO's Pharmacy Director.

PBMs: Eleven representatives of PBMs agreed to participate in an interview; however, of those eleven respondents, only two were PBMs that directly purchased prescription drugs from wholesalers or manufacturers. The interviews for one of the PBMs included five high-level executives in

²² The project team promised confidentiality to all interview respondents. Because of the small number of manufacturers of case study drugs and the small number of respondents (three manufacturers), we provide extremely limited information about the companies we spoke to and the drugs we spoke about.

pharmacy and industry relations, and at the other PBM the interview was with the director of pharmacy and the general manager.

Appendix D: Top 35 Medicare HCPCs, 2003

HCPC Code	HCPC Description	Rank \$	2003 Medicare Exp.	% of 2003 Expenditures	Study Drug	Case Study Drug
Q0136	Non ESRD epoetin alpha inj	1	\$ 1,035,540,983	9.8%	Yes	Yes
J9217	Leuprolide acetate suspension	2	\$ 726,196,566	6.9%	Yes	Yes
J7644	Ipratropium brom inh sol u d	3	\$ 725,667,328	6.9%	***	
J9310	Rituximab cancer treatment	4	\$ 580,936,425	5.5%	Yes	
J0880	Darbepoetin alfa injection	5	\$ 531,892,548	5.1%	Yes	Yes
J1745	Infliximab injection	6	\$ 495,570,356	4.7%	Yes	
J7619	Albuterol inh sol u d	7	\$ 490,536,839	4.7%	***	
J9202	Goserelin acetate implant	8	\$ 449,001,729	4.3%	Yes	Yes
J9170	Docetaxel	9	\$ 304,390,915	2.9%	Yes	
J9045	Carboplatin injection	10	\$ 269,251,108	2.6%	Yes	
J9265	Paclitaxel injection	11	\$ 260,448,815	2.5%	Yes	Yes
J3490	Drugs unclassified injection	12	\$ 255,856,152	2.4%	***	
J3487	Zoledronic acid	13	\$ 231,196,491	2.2%	Yes	
J2792	Rho (D) immune globulin h, sd	14	\$ 214,956,245	2.0%	Yes	
J9201	Gemcitabine HCl	15	\$ 204,767,764	1.9%	Yes	
Q4053	Pegfilgrastim	16	\$ 201,851,149	1.9%	***	
J9206	Irinotecan injection	17	\$ 183,148,147	1.7%	Yes	
J1563	IV immune globulin	18	\$ 173,525,870	1.6%	Yes	
J9999	Chemotherapy drug	19	\$ 166,208,940	1.6%	***	
J3395	Verteporfin injection	20	\$ 149,045,921	1.4%	**	
J1260	Dolasetron mesylate	21	\$ 142,912,265	1.4%	Yes	
J2430	Pamidronate disodium /30 MG	22	\$ 122,474,923	1.2%	Yes	
J7320	Hylan G-F 20 injection	23	\$ 112,435,690	1.1%	*	
90658	Flu vaccine, 3 yrs, im	24	\$ 103,591,765	1.0%	***	
J7517	Mycophenolate mofetil oral	25	\$ 101,528,910	1.0%	Yes	
J0151	Adenosine injection	26	\$ 94,749,452	0.9%	**	
J9355	Trastuzumab	27	\$ 89,053,943	0.8%	Yes	Yes
J7507	Tacrolimus oral per 1 MG	28	\$ 85,081,668	0.8%	Yes	
J7626	Budesonide inhalation sol	29	\$ 84,776,964	0.8%	****	
J1626	Granisetron HCl injection	30	\$ 81,894,280	0.8%	Yes	
J1441	Filgrastim 480 mcg injection	31	\$ 77,830,404	0.7%	Yes	
J9219	Leuprolide acetate implant	32	\$ 76,492,962	0.7%	Yes	
J7317	Sodium hyaluronate injection	33	\$ 66,631,851	0.6%	Yes	
J7192	Factor viii recombinant	34	\$ 58,917,219	0.6%	Yes	
J0585	Botulinum toxin a per unit	35	\$ 53,543,597	0.5%	Yes	
Total 2003 Medicare Expenditures, Top 35 HCPCs			\$ 9,001,906,184	85.6%	25 HCPCs	6 HCPCs
Total 2003 Medicare Expenditures, All HCPCs			\$ 10,518,929,270	100.0%		

Note: Medicare expenditures data was carrier paid amount for Part B drugs provided by CMS for the year 2003.

* HCPC code was excluded because HCPC was not assigned NDC-11s in the third quarter 2004 weight file.

** HCPC code was excluded because no IMS data was available for the only NDC-11 assigned to this HCPC in the third quarter 2004 weight file.

*** HCPC code was excluded as a respiratory drug, a vaccine, or because it was impossible to identify NDCs that were related to the HCPC codes.

**** HCPC code was excluded because it is rarely a physician-administered drug.

Appendix E: Subcategories of IMS' Classes of Trade

Retail Classes of Trade

Class of Trade	Subcategory
Chain	C2 - Mass merchandise/discount store with a pharmacy
	P2 - Chain pharmacy with 11 or more stores
	P3 - Chain pharmacy with 4-10 stores
	R2 - Mass merchandise/discount store without a pharmacy
	R6 - Chain HBA store without a pharmacy
	W4 - Drug chains not reporting sales to DDD
	W6 - Mass merchandise warehouse not reporting sales to DDD
	Z1 - Zip retail pharmacy
Independent	C1 - Miscellaneous retail store with a pharmacy
	P0 - Independent pharmacy located in a hospital
	P1 - Independent pharmacy
	R5 - Independent HBA store without a pharmacy
	S4 - Depot pharmacy
Foodstore	C3 - Food/convenience store with a pharmacy
	C4 - Supermarket with a pharmacy
	W5 - Grocery warehouse (non-reporting)
Mail Service	G7 - Federal government mail service pharmacy (non-reporting)
	G8 - Federal government mail service pharmacy (reporting)
	I0 - Internet Pharmacy (reporting)
	I5 - Internet Pharmacy (non-reporting)
	S5 - Mail service pharmacy (non-reporting)
	Z2 - ZIP mail service pharmacy sales (ZIP of patient)
	Z6 - ZIP mail service doctor sales (ZIP of physician)

PROVIDER PERSPECTIVE

Class of Trade	Subcategory
Non-Fed Hospitals	A2 - Non-reporting hospital/purchasing agent/ city, county, & state agencies
	A3 - Unit dose, nuclear pharmacy
	H1 - Non-federal hospitals including pharmacy depts., clinics & doctors at hospital
	H4 - Special inpatient treatment facility (hospice, drug/alcohol rehabilitation)
	W8 - Non-reporting hospital/medical/surgical supply warehouse
	Z4 - Zip hospital sales
Federal Facilities	A4 - Federal government depot/hospital agent (less than \$10,000 per month)
	F3 - Native American Indian Hospital
	F4 - Native American Indian Clinic
	G1 - US Ships
	G2 - VA hospital
	G3 - Federal government hospital (non-VA)
	G4 - Federal government (non-VA) outpatient care facility
	G6 - VA outpatient clinic/pharmacy
	S8 - Federal government depot/hospital agent (more than \$10,000 per month)

Retail Classes of Trade

<i>Class of Trade</i>	<i>Subcategory</i>
Long-Term Care	G9 - VA nursing home
	N1 - Nursing home residential care facility without a hospital
	N2 - Nursing home and institutional provider (100% of business)
	N4 - Chain nursing home provider (100% of business)
	P7 - Nursing home pharmacy (servicing multiple NHS)/purchasing services
	Z9 - Zip nursing home
HMOs	A5 - Kaiser Permanente warehouse/purchasing agent
	A6 - HMO warehouse/purchasing agent (Non-Kaiser Permanente)
	H5 - Kaiser Permanente hospital
	H7 - Kaiser Permanente pharmacy
	H8 - Kaiser Permanente clinic
	N8 - Group net pharmacy
	N9 - Group net clinic
	P8 - HMO pharmacy/HMO pharmacy depot (non-Kaiser Permanente)
	P9 - HMO clinic/HMO purchasing agent (non-hospital, non-Kaiser Permanente)
	S2 - HMO hospital (non-Kaiser Permanente)
	U0 - Workmen compensation clinic
	U3 - Union shop clinic
	U4 - Union shop pharmacy
Clinics	U8 - Workmen compensation clinic
	D1 - Outpatient clinic/doctor
	D8 - Orthopedic clinic/physician office
	D2 - Dialysis clinic/center/teaching facility
	D3 - Family planning, birth control, planned parenthood clinic
	D5 - X-ray, radiology, nephrology, urology clinic
	D6 - Oncology clinic
	D7 - Emergency center (not hospital affiliated)
	H2 - Dialysis department/center located inside a hospital or on complex
	H3 - Outpatient department/clinic/pharmacy at a hospital
	H6 - Outpatient surgical clinic (not at a hospital) including abortion, oral & plastic surgery clinics
	H9 - Outpatient PHS or disproportionate clinic
	Z3 - Zip physician sales
Home Health Care	N3 - Visiting nurse (home healthcare services)
MISCELLANEOUS	
<i>Class of Trade</i>	<i>Subcategory</i>
Prisons	M1 - City/county/state and misc. accounts (incl. city jails and juvenile detention centers)
	M2 - County/state prisons
	M3 - Federal prisons (not city jails or juvenile detention centers)
Universities	M6 - Residential school, college/university without a hospital
Other	E1 - Export company
	G5 - Federal government non-health related account (fed or military facility)
	M5 - Veterinarian, animal hospital; veterinarian supply warehouse

Retail Classes of Trade

<i>Class of Trade</i>	<i>Subcategory</i>
	R1 - Miscellaneous retail store without a pharmacy
	R3 - Food/convenience store without a pharmacy
	R4 - Supermarket without a pharmacy
	Z5 - ZIP Miscellaneous (one-time or infrequent sales)
	Z7 - ZIP nursing home patient sales (to ZIP code of patient)
	Z8 - ZIP nursing home doctor sales (to ZIP code of physician)

Source: DDD Outlet Subcategory Codes, IMS Health, October 2002.

Note: IMS defines mail-service pharmacies as a retail class of trade; however, in our analysis of the retail classes of trade combined (in Section 4) we excluded this class. Mail service pharmacies are in a separate class of trade, see different prices and are structured differently from the three retail classes of trade.

Appendix F: Average Invoice Price per Dose (AIP) by Class of Trade, 25 Study HCPCs

HCPC Code	HCPC Description	Leading Brand Name	Patent Status	All-Class AIP (not including federal facilities)	Classes of Trade											
					Retail				Mail Service	HMOs	Clinics	HHC	LTC	Hospitals	Federal Facilities	Other
					Indepen- dent	Chain	Food Stores	All Retail								
J0585	Botulinum toxin a per unit	Botox	SS	\$4.30	\$4.51	\$4.50	\$4.56	\$4.52	\$4.35	\$4.75	\$3.60	\$4.44	\$4.54	\$4.45	\$2.85	\$5.21
J0880	Darbepoetin alfa injection	Aranesp	SS	\$16.99	\$21.44	\$21.03	\$21.60	\$21.24	\$19.58	\$19.31	\$17.31	\$19.63	\$20.01	\$14.41	\$10.63	\$12.84
J1260	Dolasetron mesylate	Anzemet	SS	\$5.97	\$6.14	\$6.40	\$7.90	\$6.36	\$4.01	\$5.73	\$4.65	\$4.60	\$7.00	\$7.05	\$5.90	\$6.95
J1441	Filgrastim 480 mcg injection	Neupogen	SS	\$266.49	\$304.05	\$299.07	\$306.72	\$301.54	\$287.59	\$297.33	\$247.36	\$290.22	\$290.89	\$259.55	\$184.33	\$269.38
J1563	IV immune globulin	Multiple brands	IMS/NMS	\$40.74	\$42.20	\$55.61	\$29.15	\$42.88	\$42.10	\$50.31	\$42.16	\$43.93	\$38.37	\$39.47	\$29.17	\$49.11
J1626	Granisetron HCl injection	Kytril	SS	\$7.29	\$15.09	\$14.79	\$15.79	\$15.07	\$14.32	\$13.36	\$6.36	\$12.63	\$15.51	\$7.61	\$4.94	\$8.75
J1745	Infliximab injection	Remicade	SS	\$51.21	\$51.90	\$52.30	\$54.16	\$52.04	\$51.87	\$50.69	\$51.04	\$51.80	\$52.20	\$51.46	\$37.23	\$47.46
J2430	Pamidronate disodium /30 MG	Pamidronate Disod	IMS/NMS	\$65.79	\$140.09	\$205.48	\$242.55	\$157.76	\$141.21	\$65.11	\$62.84	\$91.24	\$115.60	\$67.26	\$51.20	\$62.12
J2792	Rho(D) immune globulin h, sd	Winrho SDF	SS/NMS	\$12.23	\$13.10	\$12.78	\$13.78	\$12.97	\$10.32	\$13.05	\$11.85	\$13.09	\$15.40	\$12.45	\$10.05	\$13.06
J3487	Zoledronic acid	Zometa	SS	\$187.69	\$198.05	\$203.06	\$203.16	\$199.51	\$195.36	\$196.05	\$186.37	\$196.13	\$204.22	\$189.89	\$132.48	\$207.31
J7192	Factor viii recombinant	Helixate FS	SS	\$831.81	\$447.83	\$968.37	\$0.00	\$468.45	\$764.14	\$1,056.04	\$742.35	\$801.05	\$1,408.50	\$880.16	\$1,009.12	\$1,546.17
J7317	Sodium hyaluronate injection	Hyalgan	IMS/NMS	\$108.84	\$115.87	\$115.51	\$116.02	\$115.68	\$111.85	\$102.92	\$107.44	\$114.92	\$115.37	\$113.74	\$86.67	\$115.77
J7507	Tacrolimus oral per 1 MG	Prograf	SS	\$3.08	\$3.20	\$3.19	\$3.22	\$3.20	\$2.97	\$3.19	\$2.52	\$3.17	\$3.18	\$3.12	\$1.86	\$2.91
J7517	Mycophenolate mofetil oral	Cellcept	SS	\$2.39	\$2.48	\$2.46	\$2.46	\$2.46	\$2.25	\$2.48	\$2.10	\$2.47	\$2.48	\$2.42	\$1.55	\$2.52
J9045	Carboplatin injection	Paraplatin	SS	\$105.36	\$129.25	\$125.25	\$141.25	\$128.63	\$127.32	\$130.84	\$99.29	\$115.72	\$131.37	\$113.68	\$65.83	\$122.87
J9170	Docetaxel	Taxotere	SS	\$276.45	\$304.46	\$300.17	\$319.31	\$303.95	\$301.38	\$289.89	\$272.45	\$298.60	\$313.47	\$286.74	\$174.59	\$266.54
J9201	Gemcitabine HCl	Gemzar	SS	\$106.28	\$110.63	\$106.15	\$111.53	\$109.84	\$107.88	\$111.08	\$106.89	\$109.76	\$112.12	\$103.99	\$65.09	\$116.62
J9202	Goserelin acetate implant	Zoladex	SS	\$192.36	\$371.79	\$354.44	\$386.76	\$364.13	\$173.35	\$246.95	\$180.79	\$346.12	\$289.99	\$228.51	\$87.27	\$345.30
J9206	Irinotecan injection	Camptosar	SS	\$117.78	\$122.33	\$121.97	\$124.36	\$122.29	\$119.13	\$121.01	\$118.01	\$121.72	\$124.86	\$116.51	\$83.71	\$121.02
J9217	Leuprolide acetate suspension	Lupron/Eligard	SS/NMS	\$245.30	\$503.40	\$565.87	\$590.25	\$543.97	\$548.08	\$258.47	\$180.15	\$568.04	\$564.80	\$341.40	\$197.50	\$351.81
J9219	Leuprolide acetate implant	Viadur	SS/IMS/NMS	\$2,534.03	\$4,735.00	\$4,820.00	\$0.00	\$4,777.50	\$4,039.53	\$0.00	\$2,192.80	\$4,689.00	\$2,498.00	\$2,213.97	\$1,155.00	\$2,592.00
J9265	Paclitaxel injection	Paclitaxel	IMS/NMS	\$20.69	\$55.28	\$77.92	\$57.27	\$58.20	\$38.86	\$47.35	\$18.67	\$23.32	\$41.15	\$21.51	\$7.14	\$24.01
J9310	Rituximab cancer treatment	Rituxan	SS	\$414.21	\$426.62	\$433.31	\$431.85	\$428.07	\$411.25	\$432.69	\$415.17	\$420.67	\$433.87	\$411.45	\$278.32	\$428.63
J9355	Trastuzumab	Herceptin	SS	\$48.84	\$53.04	\$54.60	\$55.11	\$53.38	\$49.34	\$51.71	\$48.30	\$51.53	\$52.70	\$49.29	\$33.38	\$50.49
Q0136	Non esrd epoetin alpha inj	Procrit	Co-SS	\$7.18	\$11.77	\$8.92	\$11.78	\$10.15	\$5.73	\$10.36	\$5.58	\$10.57	\$11.29	\$8.43	\$5.65	\$10.02

Source: IMS National Sales Perspective Database, Third Quarter 2004; CMS; MediSpan

Notes:

Patent Status codes are as follows: SS = single source drug products; Co-SS = co-licensed or co-marketed; IMS = innovator multi-source drug products; NMS = non-innovator multi-source (generics)
HHCs are Home Health Care facilities and LTCs are Long Term Care facilities.

Appendix G: Variation from the All-Class Average Invoice Price per Dose (AIP) by Class of Trade, 25 Study HCPCs

HCPC Code	HCPC Description	Leading Brand Name	Patent Status	Classes of Trade											
				Retail				Mail Service	HMOs	Clinics	HHC	LTC	Hospitals	Federal Facilities	Other
				Independent	Chain	Food Stores	All Retail								
J0585	Botulinum toxin a per unit	Botox	SS	5%	5%	6%	5%	1%	10%	-16%	3%	6%	3%	-34%	21%
J0880	Darbepoetin alfa injection	Aranesp	SS	26%	24%	27%	25%	15%	14%	2%	16%	18%	-15%	-37%	-24%
J1260	Dolasetron mesylate	Anzemet	SS	3%	7%	32%	7%	-33%	-4%	-22%	-23%	17%	18%	-1%	16%
J1441	Filgrastim 480 mcg injection	Neupogen	SS	14%	12%	15%	13%	8%	12%	-7%	9%	9%	-3%	-31%	1%
J1563	IV immune globulin	Multiple brands	IMS/NMS	4%	37%	-28%	5%	3%	23%	3%	8%	-6%	-3%	-28%	21%
J1626	Granisetron HCl injection	Kytril	SS	107%	103%	117%	107%	96%	83%	-13%	73%	113%	4%	-32%	20%
J1745	Infliximab injection	Remicade	SS	1%	2%	6%	2%	1%	-1%	0%	1%	2%	0%	-27%	-7%
J2430	Pamidronate disodium /30 MG	Pamidronate Disod	IMS/NMS	113%	212%	269%	140%	115%	-1%	-4%	39%	76%	2%	-22%	-6%
J2792	Rho (D) immune globulin h, sd	Winrho SDF	SS/NMS	7%	4%	13%	6%	-16%	7%	-3%	7%	26%	2%	-18%	7%
J3487	Zoledronic acid	Zometa	SS	6%	8%	8%	6%	4%	4%	-1%	4%	9%	1%	-29%	10%
J7192	Factor viii recombinant	Helixate FS	SS	-46%	16%	-100%	-44%	-8%	27%	-11%	-4%	69%	6%	21%	86%
J7317	Sodium hyaluronate injection	Hyalgan	IMS/NMS	6%	6%	7%	6%	3%	-5%	-1%	6%	6%	5%	-20%	6%
J7507	Tacrolimus oral per 1 MG	Prograf	SS	4%	4%	5%	4%	-3%	4%	-18%	3%	3%	1%	-39%	-6%
J7517	Mycophenolate mofetil oral	Cellcept	SS	4%	3%	3%	3%	-6%	3%	-12%	3%	3%	1%	-35%	5%
J9045	Carboplatin injection	Paraplatin	SS	23%	19%	34%	22%	21%	24%	-6%	10%	25%	8%	-38%	17%
J9170	Docetaxel	Taxotere	SS	10%	9%	16%	10%	9%	5%	-1%	8%	13%	4%	-37%	-4%
J9201	Gemcitabine HCl	Gemzar	SS	4%	0%	5%	3%	2%	5%	1%	3%	5%	-2%	-39%	10%
J9202	Goserelin acetate implant	Zoladex	SS	93%	84%	101%	89%	-10%	28%	-6%	80%	51%	19%	-55%	80%
J9206	Irinotecan injection	Camptosar	SS	4%	4%	6%	4%	1%	3%	0%	3%	6%	-1%	-29%	3%
J9217	Leuprolide acetate suspension	Lupron/Eligard	SS/NMS	105%	131%	141%	122%	123%	5%	-27%	132%	130%	39%	-19%	43%
J9219	Leuprolide acetate implant	Viadur	SS/IMS/NMS	87%	90%	-100%	89%	59%	-100%	-13%	85%	-1%	-13%	-54%	2%
J9265	Paclitaxel injection	Paclitaxel	IMS/NMS	167%	277%	177%	181%	88%	129%	-10%	13%	99%	4%	-66%	16%
J9310	Rituximab cancer treatment	Rituxan	SS	3%	5%	4%	3%	-1%	4%	0%	2%	5%	-1%	-33%	3%
J9355	Trastuzumab	Herceptin	SS	9%	12%	13%	9%	1%	6%	-1%	6%	8%	1%	-32%	3%
Q0136	Non esrd epoetin alpha inj	Procrit	Co-SS	64%	24%	64%	41%	-20%	44%	-22%	47%	57%	17%	-21%	40%

Source: IMS National Sales Perspective Database, Third Quarter 2004; CMS; MediSpan

Notes:

Patent Status codes are as follows: SS = single source drug products; Co-SS = co-licensed or co-marketed; IMS = innovator multi-source drug products; NMS = non-innovator multi-source (generics)

HHCs are Home Health Care facilities and LTCs are Long Term Care facilities

Appendix H: Average Invoice Price per Dose (AIP) by Major Class of Trade, Comparison of All-Class Weights and Class of Trade- Specific Weights, 25 Study HCPCs

HCPC Code	HCPC Description	Leading Brand Name	All-Class AIP (not including federal facilities)	All-Class Weights						Class-of-Trade Specific Weights						Results Differ?
				AIP by Major Class of Trade			Variation from the All-Class AIP by Class of Trade			AIP by Major Class of Trade			Variation from the All-Class AIP by Class of Trade			
				Retail	Clinic	Hospital	Retail	Clinic	Hospital	Retail	Clinic	Hospital	Retail	Clinic	Hospital	
J0585	Botulinum toxin a per unit	Botox	\$4.30	\$4.52	\$3.60	\$4.45	5%	-16%	3%	\$4.52	\$3.60	\$4.45	5%	-16%	3%	
J0880	Darbepoetin alfa injection	Aranesp	\$16.99	\$21.12	\$17.37	\$14.46	24%	2%	-15%	\$21.24	\$17.31	\$14.41	25%	2%	-15%	
J1260	Dolasetron mesylate	Anzemet	\$5.97	\$7.34	\$5.89	\$5.88	23%	-1%	-1%	\$6.36	\$4.65	\$7.05	7%	-22%	18%	Yes
J1441	Filgrastim 480 mcg injection	Neupogen	\$266.49	\$292.45	\$247.49	\$266.03	10%	-7%	0%	\$301.54	\$247.36	\$259.55	13%	-7%	-3%	
J1563	IV immune globulin	Multiple Brands	\$40.74	NA	NA	NA	NA	NA	NA	\$42.88	\$42.16	\$39.47	5%	3%	-3%	
J1626	Granisetron HCl injection	Kytril	\$7.29	\$14.28	\$6.37	\$7.49	96%	-13%	3%	\$15.07	\$6.36	\$7.61	107%	-13%	4%	Yes
J1745	Infliximab injection	Remicade	\$51.21	\$52.04	\$51.04	\$51.46	2%	0%	0%	\$52.04	\$51.04	\$51.46	2%	0%	0%	
J2430	Pamidronate disodium /30 MG	Pamidronate Disod	\$65.79	NA	\$66.83	NA	NA	2%	NA	\$157.76	\$62.84	\$67.26	140%	-4%	2%	
J2792	Rho (D) immune globulin h, sd	Winrho SDF	\$12.23	\$13.01	\$11.77	\$12.46	6%	-4%	2%	\$12.97	\$11.85	\$12.45	6%	-3%	2%	
J3487	Zoledronic acid	Zometa	\$187.69	\$199.51	\$186.37	\$189.89	6%	-1%	1%	\$199.51	\$186.37	\$189.89	6%	-1%	1%	
J7192	Factor viii recombinant	Helixate FS	\$831.81	NA	NA	NA	NA	NA	NA	\$468.45	\$742.35	\$880.16	-44%	-11%	6%	
J7317	Sodium hyaluronate injection	Hyalgan	\$108.84	\$116.13	\$107.36	\$113.69	7%	-1%	4%	\$115.68	\$107.44	\$113.74	6%	-1%	5%	
J7507	Tacrolimus oral per 1 MG	Prograf	\$3.08	\$3.20	\$2.55	\$3.00	4%	-17%	-2%	\$3.20	\$2.52	\$3.12	4%	-18%	1%	
J7517	Mycophenolate mofetil oral	Cellcept	\$2.39	\$2.46	\$2.15	NA	3%	-10%	NA	\$2.46	\$2.10	\$2.42	3%	-12%	1%	
J9045	Carboplatin injection	Paraplatin	\$105.36	NA	\$98.69	\$112.25	NA	-6%	7%	\$128.63	\$99.29	\$113.68	22%	-6%	8%	
J9170	Docetaxel	Taxotere	\$276.45	\$303.95	\$272.33	\$286.57	10%	-1%	4%	\$303.95	\$272.45	\$286.74	10%	-1%	4%	
J9201	Gemcitabine HCl	Gemzar	\$106.28	\$109.84	\$106.80	\$104.18	3%	0%	-2%	\$109.84	\$106.89	\$103.99	3%	1%	-2%	
J9202	Goserelin acetate implant	Zoladex	\$192.36	\$358.52	\$181.31	\$227.42	86%	-6%	18%	\$364.13	\$180.79	\$228.51	89%	-6%	19%	
J9206	Irinotecan injection	Camptosar	\$117.78	\$122.27	\$117.95	\$116.63	4%	0%	-1%	\$122.29	\$118.01	\$116.51	4%	0%	-1%	
J9217	Leuprolide acetate suspension	Lupron/Eligard	\$245.30	\$492.41	\$198.36	\$326.97	101%	-19%	33%	\$543.97	\$180.15	\$341.40	122%	-27%	39%	Yes
J9219	Leuprolide acetate implant	Viadur	\$2,534.03	\$4,777.50	\$2,192.80	\$2,213.97	89%	-13%	-13%	\$4,777.50	\$2,192.80	\$2,213.97	89%	-13%	-13%	
J9265	Paclitaxel injection	Paclitaxel	\$20.69	NA	\$18.74	\$22.26	NA	-9%	8%	\$58.20	\$18.67	\$21.51	181%	-10%	4%	
J9310	Rituximab cancer treatment	Rituxan	\$414.21	\$428.93	\$415.16	\$411.41	4%	0%	-1%	\$428.07	\$415.17	\$411.45	3%	0%	-1%	
J9355	Trastuzumab	Herceptin	\$48.84	\$53.38	\$48.30	\$49.29	9%	-1%	1%	\$53.38	\$48.30	\$49.29	9%	-1%	1%	
Q0136	Non esrd epoetin alpha inj	Procrit	\$7.18	\$10.06	\$5.78	\$8.16	40%	-20%	14%	\$10.15	\$5.58	\$8.43	41%	-22%	17%	

Notes:

Patent Status codes are as follows: SS = single source drug products; Co-SS = co-licensed or co-marketed; IMS = innovator multisource drug products; NMS = non-innovator multisource (generics)
The retail classes of trade are independent pharmacies, chain pharmacies and food stores.

The all-class weights reflect the shares of each NDC-11 within the HCPC for all classes of trade combined. The class-of-trade specific weights reflect the shares of each NDC-11 within the HCPC for the individual class of trade.

The indicator for whether the results differ is positive if AIP is defined for all major classes of trade and the use of class-of-trade specific weights increased the absolute value of the difference between the class-of-trade specific AIP and the all-class AIP by at least five percentage points.

EXHIBIT 3

NOTE: You must click [here](#) for very important D&B information. (/pages/db.aspx)

(/)

Search Data by Keyword Search Site



Enter Keyword

An official website of the U.S. Government

Advanced Data Search (/Pages/AdvancedSearch.aspx)

[USAspending \(/Pages/default.aspx\)](#) > Advanced Data Search

ADVANCED DATA SEARCH

Fiscal Year and Spending Type are required selections; you may select multiple filters in every category. Search results display up to 1,000,000 transactions; however, you can download all transactions. The downloaded zip file contains spreadsheets for each Spending Type selected. Sub-award data for all Spending Types is in a separate spreadsheet.

In the Search Results, click on Recipient Name to go to the Recipient Profile; click on the Award ID to see the Award Summary; click on header to sort the columns.

+ SEARCH CRITERIA

RESULTS SUMMARY

Change Search Filters ^

Filters: herceptin; Contracts, Grants, Loans, Other Financial Assistance; FY 2017, FY 2016, FY 2015, FY 2014, FY 2013, FY 2012, FY 2011, FY 2010, FY 2009, FY 2008

Total Number of Transactions

75

Total Prime Recipient Transaction Amount

\$5,309,027

Total Sub-Award Transaction Amount

\$8,429

50 Contracts

EXHIBIT 4

AWARD SUMMARY

CARDINAL HEALTH, INC.

AWARD OVERVIEW

Award Number SPM2DX10D0028
Order Number U347
Awarding Agency Department of Defense
Award Date 4/11/2012
Total Award Amount \$40,686
Total Number of Transactions 1
Total Number of Sub-Awards 0
Total Amount of Sub-Awards \$0

RECIPIENT INFORMATION

Recipient Name CARDINAL HEALTH, INC.
Recipient DUNS Number 801423062
Recipient Address 5555 GLENDON CT
Recipient City Dublin
Recipient State Ohio
Recipient Congressional District OH-12
Recipient Country United States of America
Executive Compensation Provided The Prime awardee has declared that, for this DUNS, no reporting of executive compensation is required under Section 6202 of P.L. 110-252, amending the Federal Funding Accountability and Transparency Act (P.L. 109-282).

ALL TRANSACTIONS

<< < 1 > >> Page 1 of 1

Award Number SPM2DX10D0028
Modification Number 0

EXHIBIT 5

AWARD SUMMARY

CARDINAL HEALTH, INC.

AWARD OVERVIEW

Award Number SPM2DX10D0028
Order Number BV30
Awarding Agency Department of Defense
Award Date 6/23/2014
Total Award Amount \$30,216
Total Number of Transactions 1
Total Number of Sub-Awards 0
Total Amount of Sub-Awards \$0

RECIPIENT INFORMATION

Recipient Name CARDINAL HEALTH, INC.
Recipient DUNS Number 801423062
Recipient Address 5555 GLENDON CT
Recipient City Dublin
Recipient State Ohio
Recipient Congressional District OH-12
Recipient Country United States of America
Executive Compensation Provided The Prime awardee has declared that, for this DUNS, no reporting of executive compensation is required under Section 6202 of P.L. 110-252, amending the Federal Funding Accountability and Transparency Act (P.L. 109-282).

ALL TRANSACTIONS

<< < 1 > >> Page 1 of 1

Award Number SPM2DX10D0028
Modification Number 0

EXHIBIT 6

CARDINAL HEALTH, INC.**AWARD OVERVIEW**

Award Number SPM2DX10D0028
Order Number BY81
Awarding Agency Department of Defense
Award Date 8/4/2014
Total Award Amount \$66,570
Total Number of Transactions 1
Total Number of Sub-Awards 0
Total Amount of Sub-Awards \$0

RECIPIENT INFORMATION

Recipient Name CARDINAL HEALTH, INC.
Recipient DUNS Number 801423062
Recipient Address 5555 GLENDON CT
Recipient City Dublin
Recipient State Ohio
Recipient Congressional District OH-12
Recipient Country United States of America
Executive Compensation Provided The Prime awardee has declared that, for this DUNS, no reporting of executive compensation is required under Section 6202 of P.L. 110-252, amending the Federal Funding Accountability and Transparency Act (P.L. 109-282).

ALL TRANSACTIONS**ALL SUB-AWARDS**

No Sub-Award Data

EXHIBIT 7

VA » OAL » NAC » CCST Home » Search Menu » Pharmaceutical Catalog Search » Item Details

National Acquisition Center (CCST)

Item Details: 50242-0134-68

NATIONAL DRUG CODE (NDC):	50242-0134-68
GENERIC NAME:	TRASTUZUMAB 440MG/VIL INJ
TRADE NAME:	HERCEPTIN 440MG/VIL INJ W/20ML DILUENT
VA CLASS:	ANTINEOPLASTIC,OTHER
FSS PRICE:	\$4,000.34
PRICE PER DOSAGE:	\$4,000.34
PRIME VENDOR (PV):	YES

FSS: V797D-60724, Genentech USA details

CONTRACT POINT OF CONTACT:

NAME: Kevin Mosca
 PHONE: 650-225-3206
 FAX:
 EMAIL: mosca.kevin@gene.com

CORPORATE ADDRESS:

ADDRESS: 1 DNA Way, MS 315A
 ADDRESS:
 CITY: South San Francisco
 STATE: CA
 ZIPCODE: 94080
 SITE: [Web Site](#)
 DUNS: 808043678#

SOCIOECONOMIC INFORMATION: (IF ALL FIELDS BELOW ARE BLANK THEN SIZE IS OTHER THAN SMALL)

SMALL: —
 SDB: —
 VETERAN OWNED: —
 WOMAN OWNED: —
 DISABLED VETERAN: —
 HUB ZONE: —
 8A: —

CONTRACT DATES:

AWARDED: 9/30/2016
 EFFECTIVE: 9/30/2016
 EXPIRATION: 9/29/2021

NAC CONTRACTING OFFICER (CO):

NAME: Deborah Bukowski
 PHONE: (708) 786-5219
 EMAIL: deborah.bukowski@va.gov

ORDERING CONTACT:

ADDRESS:
 CITY:
 STATE:
 ZIPCODE:
 PHONE:
 FAX:
 EMAIL:
 EMERGENCY CONTACT:
 NAME:
 PHONE:

PAYMENT/DELIVERY INFORMATION:

CREDIT CARD ACCEPTED: Yes
 CREDIT CARD DISCOUNT: None
 MINIMUM ORDER: One Unit for Direct Orders Only
 DELIVERY TERMS: 2 to 5 Days After Receipt of Order
 EXPEDITED DELIVERY: 24 hrs ARO (Mondays-Thursdays only)
 Deliveries can be made Friday and Saturday for urgent requests with no additional freight charges.

DISCOUNT INFORMATION:

PROMPT PAYMENT: 2% 30, Net 31 Days for Direct Orders Only
 QUANTITY DISCOUNT: None

WARRANTY INFORMATION:

DETAILS: Government Clause

EXHIBIT 8

Home	Getting Started	General Info	Opportunities	Agencies	Privacy
----------------------	---------------------------------	------------------------------	-------------------------------	--------------------------	-------------------------

Buyers: [Login](#) | [Register](#) Vendors: [Login](#) | [Register](#) [Accessibility](#)



65--Genetech USA, Inc 65IB Drugs, Pharmaceuticals and Hematology related products

Solicitation Number: 65
Agency: Department of Veterans Affairs
Office: VA National Acquisition Center
Location: Department of Veterans Affairs National Acquisition Center

[Notice Details](#)

[Packages](#)

[Interested Vendors List](#)

[Print](#) [Link](#)

Original Synopsis
Nov 05, 2016
11:37 am

[Return To Opportunities List](#)

Solicitation Number: 65
Notice Type: Award Notice

Contract Award Date:
September 30, 2016

Contract Award Number:
V797D-60724

Contract Award Dollar Amount:
3,850,225,230.00

Contract Line Item Number:
70

Contractor Awarded DUNS:
808043678

Contractor Awardee:
GENENTECH USA, INC;1 DNA WAY,SOUTH SAN FRANCISCO,CA;94080

Synopsis:
Added: Nov 05, 2016 11:37 am
No Description Provided

Please consult the list of [document viewers](#) if you cannot open a file.

Attachment

Type: Other (Draft RFPs/RFIs, Responses to Questions, etc..)
Posted Date: November 5, 2016

<https://www.vendorportal.ecms.va.gov/FBODocumentServ...>
Description: VA797F-16-AP-0002 V797D-60724.docx

ALL FILES

[Attachment](#)
Nov 05, 2016
[VA797F-16-AP-0002 V7...](#)

GENERAL INFORMATION

Notice Type:
Award Notice

Posted Date:
November 5, 2016

Response Date:
-

Archiving Policy:
Automatic, 15 days after award date

Archive Date:
November 29, 2016

Original Set Aside:
N/A

Set Aside:
N/A

Classification Code:
65 -- Medical, dental & veterinary equipment & supplies

NAICS Code:
325 -- Chemical Manufacturing/325412 -- Pharmaceutical Preparation Manufacturing

Additional Info:

[FSS Homepage](#)

Contracting Office Address:
Department of Veterans Affairs;OA&L / National Acquisition Center;Building 37;1st Avenue, One Block North of Cermak;Hines IL 60141

Point of Contact(s):
FSS Service Help Desk
708-786-7737
helpdesk.ammhinfss@va.gov

[FSS Help Desk Email](#)

[Return To Opportunities List](#)

[For Help: Federal Service Desk](#) [Accessibility](#)

FedBizOpps Award Notice

CLASSIFICATION CODE *	65
SUBJECT *	Genetech USA, Inc 651B Drugs, Pharmaceuticals and Hematology related products
GENERAL INFORMATION	
CONTRACTING OFFICE'S ZIP-CODE *	60141
SOLICITATION NUMBER *	65
BASE NOTICE TYPE	
ARCHIVE	60 DAYS AFTER THE AWARD DATE
RECOVERY ACT FUNDS	
NAICS CODE *	325412
SET-ASIDE	
CONTRACTING OFFICE ADDRESS	Department of Veterans Affairs OA&L / National Acquisition Center Building 37 1st Avenue, One Block North of Cermak Hines IL 60141
DESCRIPTION	See Attachment
POINT OF CONTACT * <small>(POC Information Automatically Filled from User Profile Unless Entered)</small>	FSS Service Help Desk 708-786-7737 helpdesk.ammhinfss@va.gov
AWARD INFORMATION	
AWARD NUMBER *	V797D-60724
AWARD AMOUNT *	3,850,225,230.00
LINE ITEM NUMBER	70
AWARD DATE (MM-DD-YYYY) *	09-30-2016
AWARDEE NAME *	GENENTECH USA, INC
CONTRACTOR'S DUNS NUMBER	808043678
AWARDEE ADDRESS LINE 1 *	
AWARDEE ADDRESS LINE 2 *	
AWARDEE ADDRESS LINE 3 *	1 DNA WAY
AWARDEE ADDRESS LINE 4 *	
AWARDEE CITY	SOUTH SAN FRANCISCO
AWARDEE STATE	CA
AWARDEE ZIP CODE	94080
ADDITIONAL INFORMATION	
AGENCY'S URL	www.fss.va.gov
URL DESCRIPTION	FSS Homepage
AGENCY CONTACT'S EMAIL ADDRESS	FSS.Help@va.gov
EMAIL DESCRIPTION	FSS Help Desk Email

* = Required Field

FedBizOpps Award Notice
Rev. March 2010

EXHIBIT 9

Trastuzumab (Herceptin®)**National Drug Monograph****December 2014****VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives**

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information¹**Description/Mechanism of Action**

Trastuzumab is a HER2/neu receptor antagonist that mediates antibody-dependent cellular cytotoxicity on HER2 overexpressing tumor cells.

Indication(s) Under Review in this document (may include off label)

Metastatic Breast Cancer (1998): trastuzumab is FDA approved

- In combination with paclitaxel for first-line treatment of HER2-over-expressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease

Adjuvant Breast Cancer (2006): trastuzumab is FDA approved for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature breast cancer

- As part of a treatment regimen consisting of doxorubicin, cyclophosphamide and either paclitaxel or docetaxel
- With docetaxel and carboplatin
- As a single agent following multi-modality anthracycline-based therapy

Metastatic Gastric Cancer (2013): trastuzumab is FDA approved in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease

Dosage Form(s) Under Review

Available a lyophilized powder of 440 mg in a multidose vial

REMS

☐ REMS ☒ No REMS ☐ Postmarketing Requirements
See Other Considerations for additional REMS information

Pregnancy Rating

Pregnancy Category D

Background**Purpose for review**

FDA-approval in 1998 (prior to current formulary review process)

Issues to be determined:

What role does trastuzumab have in HER2 overexpressing breast and gastric cancers?

What safety issues need to be considered?

Other therapeutic options**Formulary Alternatives
HER2-directed agents****Other Considerations**

None

**Non-formulary Alternatives
HER2-directed agents****Other Considerations**

December 2014

Updated version may be found at www.pbm.va.gov or vawww.pbm.va.gov

Lapatinib	Oral formulation; TKI against EGFR1 and HER2
Pertuzumab	Injectable; administered in combination with trastuzumab
Ado-trastuzumab emtansine	Injectable; Antibody-Drug Conjugate; activity post-trastuzumab

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline with focus over the last 10 years using the search terms: meta-analysis, trastuzumab, adjuvant therapy, early breast cancer, metastatic breast cancer, metastatic gastric cancer. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy

Trastuzumab (H) in the Adjuvant Treatment of HER2-Positive Early Breast Cancer (Refer to Table 1)

- A meta-analysis of RCTs was performed to compare adjuvant trastuzumab therapy to observation for patients with HER2-positive early breast cancer. Viani, et al. identified five randomized trials for inclusion. The analysis indicated there was a significant improvement in mortality, recurrence, metastases and secondary tumors (other than breast) with one year of trastuzumab therapy. Cardiac toxicity and brain metastases were significantly more common among those receiving trastuzumab.²
- Yin, et al. performed a meta-analysis to assess the benefits of concurrent vs. sequential trastuzumab with adjuvant therapy. Utilizing six eligible studies, the analysis indicates that trastuzumab provided benefit with regard to DFS, OS, locoregional and distant recurrence. CNS recurrence rate was higher in those receiving trastuzumab. Patients receiving concomitant trastuzumab had statistically significant improvements in OS while a higher incidence of CNS recurrence, as compared to the sequential trastuzumab patients who did not achieve significance with regard to OS or CNS recurrence. These findings suggest that concomitant trastuzumab is superior to sequential, with the possibility that CNS recurrence is secondary to prolonged survival.³
- A Cochrane review of trastuzumab-containing regimens for early breast cancer included eight trials and a total of 11,991 patients. The intent of the analysis was to evaluate the evidence of efficacy and safety with trastuzumab in the adjuvant setting and its relation to duration and schedule of administration (concurrent vs. sequential). The authors concluded that overall trastuzumab significantly improved OS and DFS in HER2-positive women with early stage breast cancer. Cardiovascular risk, in term of increased risk of CHF and LVEF decline, is increased with trastuzumab therapy. Due to the small numbers of included studies, no conclusions can be made about the schedule of administration.⁴

Table 1. Meta-analyses (MA) of Adjuvant Trastuzumab (H) in Early Breast Cancer (EBC)

Citation	HERA	BCIRG 006	FinHer	NCCTG N9831	NSABP B31	PACS 04	NOAH	Buzdar	Results
Viani, 2007 ² MA of RCTs comparing adjuvant H vs. obs 5 trials: N= 9117	X	X	X	X	X				Adjuvant H vs. obs in EBC Mortality rate (p<0.00001) Recurrence rate (p<0.00001) Second other tumors (p=0.007) Metastases rate (p<0.00001) CV tox (grade 3,4): 4.5 vs. 1.8% Brain mets: 54 vs. 30 events; OR 1.82
Yin, 2011 ³ MA of RCTs evaluating adjuvant chemo with (concurrent vs. sequential) H vs. no H 6 trials; N = 13,952	X	X	X	X	X	X			Adjuvant H (Concur vs. Seq) vs. control DFS: OR 0.69 (0.59-0.80); p<0.001 OS: OR 0.69 (0.58-0.83) vs. 0.86 (0.73-1.01) CNS Recurrence rate: OR 1.58 (1.08-2.30) Distant recurrence: OR 0.62 (0.55-0.69)
Moja, 2012 ⁴ MA of RCTs evaluating efficacy & safety of H in adjuvant or neo-adjuvant setting of EBC 8 trials; N= 11,991	X	X	X	X	X	X	X	X	Adjuvant H (Concur vs. Seq) vs. control OS: HR 0.66 (0.57-0.77); p<0.00001 DFS: HR 0.60 (0.50-0.71); p<0.00001 Risk of CHF: RR 5.11 (90% CI: 3-8.72); p<0.00001 Risk of ↓LVEF: RR 1.83 (90% CI: 1.36-2.47); p=0.0008

Trastuzumab (H) in the Treatment of HER2-Positive Metastatic Breast Cancer

A Cochrane review was performed to evaluate the safety and efficacy of trastuzumab in the metastatic breast cancer setting. The review included RCTs that evaluated trastuzumab alone or in combination with cytotoxic chemotherapy or hormonal therapy. A total of 7 trials with 1497 patients met the inclusion criterion. For the endpoint of OS, five of 7 trials reported this outcome with an improvement in overall survival by 5-8 months in the trastuzumab-containing arms compared to control arms OS [HR 0.82 (0.71-0.94) p=0.004]. Three trials evaluated trastuzumab in the first-line MBC setting, while two trials considered trastuzumab beyond progression. OS was improved in the first-line setting [HR 0.79 (0.67-0.94); p=0.006], while OS beyond progression was not significantly different [HR 0.87 (0.68-1.12) p=0.27]. Progression-free survival (PFS) was evaluated in all 7 trials. Trastuzumab extended PFS from 2-11 months compared to control [HR 0.61 (0.54-0.70) p<0.00001]. The benefit was noted as significant whether trastuzumab was given in the first-line or beyond progression setting.⁵

Trastuzumab (H) in the Treatment of HER2-Positive Metastatic Gastric Cancer

FDA-approval of trastuzumab for the treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma comes from the ToGA (Trastuzumab for Gastric Cancer) trial. In an open-label, international (including Asia, Central and South America, Europe), phase 3 RCT, patients with overexpressed HER2 gastric or GEJ cancer who had not received previous treatment, were randomized 1:1 to either trastuzumab + chemotherapy (capecitabine + cisplatin or 5-fluorouracil + cisplatin) vs. chemotherapy alone. The primary endpoint of OS was significantly improved with the addition of trastuzumab compared to chemotherapy alone, 13.8 vs. 11.1 months [HR 0.74 (0.60-0.91); $p=0.0046$]. Median PFS was also improved, 6.7 vs. 5.5 months, respectively [HR 0.71 (0.59-0.85); $p=0.0002$]. A pre-planned exploratory analysis evaluating degree of HER2 expression and response suggested that the improvement in OS with trastuzumab was greater in those with higher expression of the HER2 protein (IHC 2+/FISH positive or IHC 3+), compared to those with low expression (IHC 0 or 1+/FISH positive) with median OS 16 months vs. 11.8 months [HR 0.65 (0.51-0.83)].⁶

Potential Off-Label Use

The following trials can be found in www.clinicaltrials.gov unless otherwise noted:

- Intrathecal trastuzumab trials for the treatment of leptomeningeal metastases and carcinomatous meningitis in breast cancer.
- A Phase III Clinical Trial to Evaluate Patient's Preference of Subcutaneous Trastuzumab (SC) Versus Intravenous (IV) Administration in Patients with HER2 Positive Advanced Breast Cancer (ABC).
- Everolimus, Letrozole and Trastuzumab in HR- and HER2/Neu-positive Breast Cancer Patients
- Evaluation of Carboplatin/Paclitaxel With and Without Trastuzumab (Herceptin) in Uterine Serous Cancer
- Efficacy and Safety Study of Trastuzumab, Paclitaxel and Carboplatin on HER2+ Preoperative Breast Cancer
- Evidence to support the addition of HER2-directed agents to neoadjuvant therapy in HER2-positive breast cancer is based upon the primary endpoint of pathologic complete response rate (pCR). Evidence from the NOAH trial (neoadjuvant chemotherapy with trastuzumab trial), which compared 1 year of treatment with trastuzumab (neoadjuvant and adjuvant) with no trastuzumab showed that 3-year event-free survival was improved with trastuzumab [71 vs. 56%; HR 0.59 (0.38-0.90); $p=0.013$]. Follow-up to this trial was presented at the ASCO 2013 Annual Meeting. After a median follow-up of 5.4 years, the benefit of improved EFS with trastuzumab was confirmed. The authors note a trend in improved OS.^{7,8}
- Use of trastuzumab in combination with chemotherapy regimens other than cisplatin and a fluoropyrimidine for first-line treatment of gastric or GEJ cancer. An observational study was conducted to evaluate the use of trastuzumab in HER2-positive metastatic gastric cancer. Data from a total of 110 patients was collected over a 2-year period. Only 28% of the population received trastuzumab as labeled with cisplatin and 5-FU or capecitabine. The rest of the patients received the following regimens: cisplatin, 5-FU, leucovorin (17%); 5-FU, leucovorin, oxaliplatin and docetaxel (8%), 5-FU, leucovorin and oxaliplatin (7%), capecitabine (6%) or other combinations (25%). The preliminary PFS was 6.8 months, which the authors note, is consistent with the 6.7 month PFS noted in the ToGA trial.⁹
- Use of trastuzumab in Non-Small Cell Lung Cancer is categorized as an NCCN 2B recommendation (defined as based upon low level of evidence with consensus that the intervention is appropriate) for patients with HER2 mutations.¹⁸

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	<ul style="list-style-type: none"> • Cardiomyopathy: Trastuzumab can result in sub-clinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue trastuzumab for cardiomyopathy. • Infusion reactions, pulmonary toxicity: Discontinue trastuzumab for anaphylaxis, angioedema, interstitial pneumonitis or acute respiratory distress syndrome. • Embryo-Fetal Toxicity: Exposure to trastuzumab during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death.
Contraindications	<ul style="list-style-type: none"> • None
Warnings/Precautions	<ul style="list-style-type: none"> • Cardiomyopathy. Trastuzumab can cause LV cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy and cardiac death; asymptomatic declines in LVEF are also known effects; the highest incidence of cardiac dysfunction is noted when trastuzumab is given with an anthracycline. Trastuzumab should be withheld in situations where there is $\geq 16\%$ absolute decrease in LVEF from baseline values or an LVEF value that is below institutional limits of normal and $\geq 10\%$ absolute decrease from baseline values. The following monitoring schedule is recommended: <ul style="list-style-type: none"> ○ Baseline cardiac assessment including history, physical exam and LVEF via echocardiogram or MUGA scan ○ Baseline LVEF immediately prior to start of trastuzumab ○ LVEF every 3 months during and upon completion of trastuzumab ○ LVEF at 4-week intervals if trastuzumab is held for significant LV dysfunction ○ LVEF every 6 months for at least 2 years following completion of trastuzumab for adjuvant therapy • Infusion Reactions. Serious and fatal infusion reactions have been reported among postmarketing data. Severe reactions may include bronchospasm, anaphylaxis, angioedema, hypoxia and severe hypotension. The onset and clinical course of the reactions are variable. Fatalities occurred within hours to days following a serious reaction. Trastuzumab should be interrupted in all patients that experience dyspnea and significant hypotension. Emergent medical therapy may be needed, such as epinephrine, corticosteroids, diphenhydramine, bronchodilators and oxygen. Monitor and evaluate patients until complete resolution of all signs and symptoms. Permanent discontinuation should be considered in all patients with severe infusion reactions. Pre-medication with antihistamines and/or corticosteroids should be considered if therapy is to resume, recognizing that recurrent reactions are possible despite pre-medication. • Embryo-fetal Toxicity. Trastuzumab can cause fetal harm when administered to a pregnant woman. Cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities and neonatal death have been noted in post-marketing reports. Women of child-bearing potential should be advised of the potential hazard to the fetus resulting from trastuzumab exposure during pregnancy and provided contraception counseling. • Pulmonary Toxicity. Trastuzumab use can result in serious and fatal pulmonary toxicity. Pulmonary toxicity can occur as sequelae of an infusion reaction. Those with symptomatic intrinsic lung disease or extensive tumor

involvement of the lungs, that results in dyspnea at rest, appear to experience greater lung toxicity.

- Exacerbation of Chemotherapy-induced Neutropenia. The incidences of Grade 3 or 4 neutropenia and febrile neutropenia were higher in the patients who received trastuzumab and myelosuppressive chemotherapy compared to those who received chemotherapy alone.
 - HER2 Testing. HER2 protein overexpression is necessary for patient selection for trastuzumab therapy as these are the only patients studied and for whom a benefit has been shown. Use FDA-approved tests for the specific tumor types (breast vs. gastric) as there are differences in the tumor histopathology. HER2 status should be performed by laboratories proficient in utilizing FDA-approved tests to obtain reliable results.
-

Safety Considerations

- HER2 testing is essential to determine if patients are appropriate for trastuzumab therapy. Selected laboratories need to be proficient with IHC and FISH technology to ensure reliable results.
- Look Alike Sound Alike potential for medication errors due to similarity in names between trastuzumab and ado-trastuzumab emtansine.
- Risk for cardiomyopathy and potential for reduced LVEF are major considerations prior to initiation of trastuzumab therapy. Whether trastuzumab is administered as a single agent or as part of a treatment plan that includes anthracyclines, some degree of myocardial dysfunction can be expected. Appropriate cardiac monitoring is essential throughout the course of therapy.
- Risk of embryo-fetal toxicity, as exposure can result in embryo-fetal death or birth defects. Advise patients of these risks and the need for effective contraception. Perform a pregnancy test before initiating therapy in women of childbearing potential and periodically throughout treatment if risk of pregnancy is questionable.
- Trastuzumab can potentiate the risk of chemotherapy-induced neutropenia when given as part of a treatment plan that includes myelosuppressive chemotherapy. Anticipation of Grade 3, 4 neutropenia and possibly febrile neutropenia should be a consideration prior to initiating therapy with trastuzumab and chemotherapy.
- Infusion-related reactions can be severe and fatal. The onset and clinical course of these reactions has been variable. Trastuzumab infusions should be interrupted for symptomatic patients with careful monitoring until complete resolution. Pre-medication with antihistamines and/or corticosteroids may need to be considered.
- Within the Cochrane review in MBC, all 7 trials reported data on cardiovascular events. Congestive heart failure and cardiac dysfunction NYHA class III and IV events were combined. Overall, trastuzumab use was associated with an increased risk of severe cardiac events [RR 3.49 (1.88-6.47) p=0.0009]. When comparing the type of regimen with cardiac toxicity, trastuzumab with an anthracycline significantly increased risk [RR 5.43 (90% CI 2.28-12.94) p=0.001]. Evaluation of LVEF decline was reported in 6 trials. The pooled analysis indicates an increased risk of decline with trastuzumab [RR 2.65 (90% CI 1.48-4.74) p=0.006]. Risk of LVEF decline was noted in both first-line and beyond-progression settings.⁵
- The ToGA trial reported that Trastuzumab + chemotherapy vs. chemotherapy alone had similar adverse effect profiles. Nausea, neutropenia, vomiting and anorexia were the most common reported events. Grade 3 or 4 events were similar, except for diarrhea, which was reported in a higher number of trastuzumab patients (9 vs. 4%). Rates of grade 3 or 4 cardiac events were similar between both groups and were noted in a minority of patients (6 vs. 6%).⁶
- Use of intrathecal trastuzumab (off-label) will require drug reconstitution with preservative-free diluent, NOT the diluent included from the manufacturer in packaging, which contains 1.1% benzyl alcohol.

Adverse Reactions

Common adverse reactions	Adjuvant and metastatic breast cancer setting: fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, myalgia Metastatic gastric cancer setting: neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, dysgeusia
Death/Serious adverse reactions	Severe infusion reactions, neutropenia, infection/febrile neutropenia, pulmonary toxicity, diarrhea, CHF or symptomatic decrease in LVEF
Discontinuations due to adverse reactions	Adjuvant and metastatic breast cancer setting: CHF, significant decline in LV cardiac function, severe infusion reactions, pulmonary toxicity Metastatic gastric cancer setting: infection, diarrhea, febrile neutropenia

Drug Interactions**Drug-Drug Interactions**

- Anthracyclines (doxorubicin, epirubicin, etc.): Avoid use with trastuzumab due to potential of increasing risk of cardiotoxicity.
- Paclitaxel: Mean serum concentration of trastuzumab is increased when administered with paclitaxel.
- Myelosuppressive chemotherapy: Trastuzumab therapy can increase risk of neutropenia.

Risk Evaluation

As of November 24, 2014

Comments																
Sentinel event advisories	<ul style="list-style-type: none">No sentinel event advisories. Alerts are related to the name similarity between trastuzumab and ado-trastuzumab emtansine.Sources: ISMP, FDA, TJC															
Look-alike/sound-alike error potentials	<ul style="list-style-type: none">Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List) <table><tr><th>NME Drug Name</th><th>Lexi-Comp</th><th>First DataBank</th><th>ISMP</th><th>Clinical Judgment</th></tr><tr><td>Trastuzumab 440mg MDV</td><td>Ado-trastuzumab emtansine Pertuzumab</td><td>None</td><td>Ado-trastuzumab emtansine</td><td>Alemtuzumab Tocilizumab Trametinib</td></tr><tr><td>Herceptin</td><td>None</td><td>None</td><td>None</td><td>Heparin Hepsera Hespan</td></tr></table> <p>Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)</p> <p>!High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.</p>	NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment	Trastuzumab 440mg MDV	Ado-trastuzumab emtansine Pertuzumab	None	Ado-trastuzumab emtansine	Alemtuzumab Tocilizumab Trametinib	Herceptin	None	None	None	Heparin Hepsera Hespan
NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment												
Trastuzumab 440mg MDV	Ado-trastuzumab emtansine Pertuzumab	None	Ado-trastuzumab emtansine	Alemtuzumab Tocilizumab Trametinib												
Herceptin	None	None	None	Heparin Hepsera Hespan												

Other Considerations

General

- HER2 testing is essential to determine if patients are appropriate for trastuzumab therapy in any setting. Selected laboratories need to be proficient with IHC and FISH technology to ensure reliable results in both breast and gastric/GEJ cancer settings.^{10, 15}
- Look Alike Sound Alike potential for medication errors due to similarity in names between trastuzumab and ado-trastuzumab emtansine.

Neoadjuvant / Adjuvant Therapy

- The VHA UNDER SECRETARY FOR HEALTH'S INFORMATION LETTER Guidance on Breast Cancer Care (draft dated 10-2014) states that trastuzumab should be considered for all patients with HER2 amplified or over-expressed breast cancer in the adjuvant setting, except for very low risk disease. Current data support the optimal duration of trastuzumab treatment is one year.¹¹
- The National Comprehensive Cancer Network (NCCN) Guidelines include trastuzumab as a component of adjuvant therapy (Category 1 recommendation) in HER2-positive tumors that are either node-positive or node-negative with tumor > 1 cm.¹²
- The National Institute for Health and Care Excellence (NICE) evidence review group summarized the clinical and cost-effectiveness of trastuzumab in HER2-positive primary breast cancer, supporting the use of trastuzumab for one year or until disease recurrence in patients following surgery, chemotherapy and radiotherapy.¹³

MBC Setting

- The American Society of Clinical Oncology (ASCO) Guidelines on Systemic therapy for patients with advanced HER2-positive breast cancer support the use of HER2-targeted therapy-based combinations as first-line, second-line and third-line treatment.¹⁴
Evidence GRADE. First-line setting. Evidence quality: high; strength of recommendation: strong
Evidence GRADE. Second-line setting. Evidence quality: high; strength of recommendation: strong
Evidence GRADE. Third-line setting. Evidence quality: intermediate; strength of recommendation: moderate
- The combination of trastuzumab, pertuzumab and a taxane is recommended for first-line therapy, unless contraindication to taxanes exist.
Evidence GRADE. Evidence quality: high; strength of recommendation: strong
- The National Comprehensive Cancer Network (NCCN) Guidelines include trastuzumab either alone or in combination with other agents in the recurrent or metastatic breast cancer setting. A Category 1 recommendation is given to the combination of pertuzumab, trastuzumab and docetaxel as a preferred first-line regimen in this setting. Trastuzumab alone or in combination with other cytotoxic agents are given a Category 2A recommendation.¹²
- The optimal duration and ideal sequence of HER2-targeted therapy in MBC is unknown at this time.

Gastric/Gastroesophageal Junction Adenocarcinoma Setting

- The benefit of trastuzumab correlated with strong positivity of HER2 status.⁶
- FDA approval is based upon use of trastuzumab with a cisplatin and fluoropyrimidine-based regimen. NCCN guidelines categorize a cisplatin/fluoropyrimidine-based regimen as Category 1, while other active regimens are Category 2A.¹⁶

Dosing and Administration

- Refer to the package insert for full dosing information.

Special Populations (Adults)

	Comments
Elderly	<ul style="list-style-type: none"> • Among the adjuvant and metastatic breast cancer trials, the risk of cardiac dysfunction was increased in patients over age 65 years compared to younger patients. The reported clinical experience in breast cancer is not adequate to determine if there is a difference between young and old populations. • No differences in safety or effectiveness were noted between elderly and young patients in the metastatic gastric cancer setting.
Pregnancy	<ul style="list-style-type: none"> • Pregnancy Category D. Fetal harm can result when trastuzumab is given to a pregnant woman. Cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities and neonatal death have been noted in post-marketing reports. Monitor pregnant women exposed to trastuzumab for oligohydramnios. Consider fetal testing appropriate for gestational age and consistent with community standards. Advise women of the potential of harm to her fetus subsequent to trastuzumab exposure.
Lactation	<ul style="list-style-type: none"> • It is not known if trastuzumab is excreted in human milk, but IgG is; a decision concerning the importance of the drug to the mother with the potential risk to the nursing infant should be addressed.
Renal Impairment	<ul style="list-style-type: none"> • No specific recommendations for renal impairment have been noted; renal toxicity was identified in the metastatic gastric cancer trial as well as rare cases of nephrotic syndrome identified through post-marketing studies.
Hepatic Impairment	<ul style="list-style-type: none"> • No data identified.
Pharmacogenetics/genomics	<ul style="list-style-type: none"> • No data identified.

Projected Place in Therapy

Adjuvant Therapy Setting in EBC

- The VHA UNDER SECRETARY FOR HEALTH'S INFORMATION LETTER Guidance on Breast Cancer Care (draft dated 10-2014) states that trastuzumab should be considered for all patients with HER2 amplified or over-expressed breast cancer in the adjuvant setting, except for very low risk disease. Current data support the optimal duration of trastuzumab treatment is one year.
- The National Comprehensive Cancer Network (NCCN) Guidelines include trastuzumab as a component of adjuvant therapy (Category 1 recommendation) in HER2-positive tumors that are either node-positive or node-negative with tumor > 1 cm.

Neoadjuvant (Preoperative) Therapy Setting in EBC

- Evidence to support the addition of HER2-directed agents to neoadjuvant therapy in HER2-positive breast cancer is based upon the primary endpoint of pathologic complete response rate (pCR).

MBC Setting

- The American Society of Clinical Oncology (ASCO) Guidelines on Systemic therapy for patients with advanced HER2-positive breast cancer support the use of HER2-targeted therapy-based combinations as first-line, second-line and third-line treatment.¹⁴
- The National Comprehensive Cancer Network (NCCN) Guidelines include trastuzumab either alone or in combination with other agents in the recurrent or metastatic breast cancer setting. A Category 1 recommendation is given to the combination of pertuzumab, trastuzumab and docetaxel as a preferred first-line regimen in this setting. Trastuzumab alone or in combination with other cytotoxic agents are given a Category 2A recommendation.¹²

Metastatic Gastric/GEJ Adenocarcinoma Setting

- FDA approval is based upon use of trastuzumab with a cisplatin and fluoropyrimidine-based regimen. NCCN guidelines categorize a cisplatin/fluoropyrimidine-based regimen as Category 1, while other active regimens are Category 2A.

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation Description

High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. *Ann Intern Med* 2010;153:194-199.

STRICTLY CONFIDENTIAL PRE-DECISIONAL DELIBERATION
INFORMATION

Trastuzumab Monograph

Appendix B: Approval Endpoints (use for oncology NMEs)

Table 1. A Comparison of Important Cancer Approval Endpoints

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall Survival	Clinical benefit for regular approval	<ul style="list-style-type: none"> • Randomized studies essential • Blinding not essential 	<ul style="list-style-type: none"> • Universally accepted direct measure of benefit • Easily measured • Precisely measured 	<ul style="list-style-type: none"> • May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes noncancer deaths
Symptom Endpoints (patient-reported outcomes)	Clinical benefit for regular approval	<ul style="list-style-type: none"> • Randomized blinded studies 	<ul style="list-style-type: none"> • Patient perspective of direct clinical benefit 	<ul style="list-style-type: none"> • Blinding is often difficult • Data are frequently missing or incomplete • Clinical significance of small changes is unknown • Multiple analyses • Lack of validated instruments
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> • Randomized studies essential • Blinding preferred • Blinded review recommended 	<ul style="list-style-type: none"> • Smaller sample size and shorter follow-up necessary compared with survival studies 	<ul style="list-style-type: none"> • Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias, particularly in open-label studies • Definitions vary among studies
Objective Response Rate	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> • Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended 	<ul style="list-style-type: none"> • Can be assessed in single-arm studies • Assessed earlier and in smaller studies compared with survival studies • Effect attributable to drug, not natural history 	<ul style="list-style-type: none"> • Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Only a subset of patients with benefit
Complete Response	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> • Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended 	<ul style="list-style-type: none"> • Can be assessed in single-arm studies • Durable complete responses can represent clinical benefit • Assessed earlier and in smaller studies compared with survival studies 	<ul style="list-style-type: none"> • Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Small subset of patients with benefit
Progression- Free Survival (includes all deaths) or Time to Progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> • Randomized studies essential • Blinding preferred • Blinded review recommended 	<ul style="list-style-type: none"> • Smaller sample size and shorter follow-up necessary compared with survival studies • Measurement of stable disease included • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment 	<ul style="list-style-type: none"> • Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Involves balanced timing of assessments among treatment arms

*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2007.

EXHIBIT 10

Hope this helps.

Jeff

Subject: Content of Herceptin vials
Date: Wed, 25 Sep 2002 11:52:19 -0700
From: Tom White <twite@gene.COM>
Organization: Genentech, Inc.
To: Olivia Ware <ware.olivia@gene.COM>
CC: William Henry Smith <smith.william@gene.COM>

Genentech's Herceptin Production Engineer

The following data should correct the misconception of the pharmacy department at US Oncology that we are not filling 440 mg of Herceptin in our vials. Their assumption is based on the package insert statement that the concentration of Herceptin in the vial is 21 mg/ml and it is reconstituted with 20 ml of diluent.

$(21 \times 20 + 0.5 \text{ ml} = 409.5 \text{ to } 430.5 \text{ mg})$

In actuality we fill 18 ml of bulk solution at a concentration of 25

mg/ml into the vial and lyophilize. We therefore target 450 mg in a vial (and nominally state 440 mg). $(18 \times 25 = 450 \text{ mg})$

Our technical report supporting the IND Studies of Lyophilized Multi-dose Her2 Formulation written in 1996 states that the reconstituted volume after adding 20 ml of diluent is actually about 20.6 ml due to the volume expansion of the solids present in the vial. Hence the theoretical concentration of the reconstituted product is actually 21.8 mg/ml. $(450 \text{ mg}/20.6 \text{ ml} = 21.8 \text{ mg/ml})$ After internal discussion in 1996, it was decided to round down the concentration in the insert to the nearest whole number rather than round up to a concentration we in fact do not achieve (ie. 22mg/ml). I believe this is the source of the confusion.

Whereas we actually have between 440 and 450 mg in our vials they calculate that it is less.

$(21.8 \text{ mg/ml} \times 20.6 \text{ ml})$ vs $(21 \text{ mg/ml} \times 20 \text{ ml})$

Let me know if this fully addresses their concern or if further explanation is necessary.

*

EXHIBIT 11

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UNITED STATES DISTRICT COURT FOR THE
NORTHERN DISTRICT OF OKLAHOMA

IN RE: GENENTECH HERCEPTIN)
(TRASTUZUMAB) MARKETING AND) Case No. 16-MD-2700-TCK-TLW
SALES PRACTICES LITIGATION.) ALL CASES

TRANSCRIPT OF RECORDED PROCEEDINGS
NOVEMBER 17, 2016
BEFORE THE HONORABLE T. LANE WILSON, MAGISTRATE JUDGE PRESIDING
MOTION HEARING

Greg Bloxom, RMR, CRR
United States Court Reporter
Northern District of Oklahoma

1 submit proposed changes for approval to the FDA. That's what
2 that document shows.

3 **THE COURT:** Okay. Right, right, but let me --

4 **MS. DONAHUE:** So let me just finish. Sorry. I'm
5 sorry. I'll get to your point. So my point would be that, two
6 things. Number one, complaints about, "We're not getting, you
7 know, the 440 from a customer, from anyone, or internal
8 communications that Genentech somehow knew because it did that
9 people were complaining about that," we've produced to them
10 certificates of analysis that show that in every lot released
11 in the United States, we were below 440. Almost every. Ninety
12 percent, I think they said. So we knew. I mean, what they
13 want goes to notice and knowledge, and I think to the extent
14 that's an issue, which it's not under obstacle preemption, is
15 what he just said, but, you know, they have that evidence. So
16 what more do they need? I mean, we produced our own
17 manufacturing documents that show we're below 440, in their
18 words, 90 percent of the time.

19 **THE COURT:** All right. Let me get back to -- I
20 understand what you're saying, but let me get back to my
21 question. Okay. So think of the worst document that could be
22 in the files that Mr. Keglovits says he's looking for, and your
23 position is, "I don't care how bad that document is, it doesn't
24 matter, this is a legal issue and we win." I mean, am I right
25 about that?